# STIC Search Report
## Biotech-Chem Library

STIC Database Tracking Number: 133115

| | |
|---|---|
| **TO: Dwayne C Jones**<br>**Location: REM-3B87&3C70**<br>**Art Unit: 1614**<br>**Tuesday, September 28, 2004**<br><br>**Case Serial Number: 10/758415** | **From: Barb O'Bryen**<br>**Location: Biotech-Chem Library**<br>**Remsen 1A69**<br>**Phone: 571-272-2518**<br><br>**barbara.obryen@uspto.gov** |

## Search Notes

"Please search claims 1,2,8,10,11"

We claim:

1. A method for treating a polyglutamine disease, comprising administering a compound selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine, to a patient in need of such treatment.

2. The method according to claim 1, wherein said polyglutamine disease is selected from the group consisting of Huntington's disease, spinocerebellar ataxia, and spinobulbar muscular atrophy.

3. The method according to claim 1, wherein said compound is L-methionine S-sulfoximine or L-ethionine S-sulfoximine administered orally, intravenously, or intrathecally.

4. The method according to claim 1, wherein said L-methionine S-sulfoximine or L-ethionine S-sulfoximine is administered intrathecally at a dosage between 1.0-5.0 mg/kg per 6-10 days.

5. The method according to claim 1, wherein said L-methionine S-sulfoximine or L-ethionine S-sulfoximine is administered orally or intravenously at a dose between 2.0-10.0 mg/kg per 6-10 days.

6. The method according to claim 1, wherein said compound is glufosinate administered intrathecally at a dose of 1.0 – 5.0 mg per 6 -10 days.

7. The method according to claim 1, wherein said compound is an α-keto acid derived from leucine, isoleucine or valine.

8. The method according to claim 7, wherein said α-keto acid is selected from the group consisting of α-keto-isocaproate, α-keto-β-methylbutyrate and α-keto-valerate and salts thereof.

9. The method according to claim 7, wherein said α-keto acid is administered in a dosage between 280-380 mg/kg body weight.

10. The method according to claim 1, further comprising administering a second compound which inhibits aggregate formation, inhibits transglutaminase, inhibits caspase, or is neuroprotective.

11. The method according to claim 10, wherein said second compound is selected from the group consisting of Congo red, cystamine, cysteamine, minocycline, ethyl eicosapentaenoate, and riluzole.

12. A composition comprising a) an amount of a compound, selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine,

glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine, effective to treat a polyglutamine disease, b) a second neuroprotective compound, and c) a pharmaceutically acceptable carrier.

13. The composition according to claim 12, wherein said second neuroprotective compound inhibits: aggregate formation, transglutaminase and/or caspase.

14. The composition according to claim 12 wherein said second compound is selected from the group consisting of Congo red, cystamine, cysteamine, minocycline, ethyl eicosapentaenoate, riluzole, L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine.

15. A kit comprising two or more compounds selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine, in separate containers.

16. The kit according to claim 15, further comprising another compound useful for the treatment of polyglutamine diseases.

17. The kit according to claim 16, wherein said compound useful for the treatment of polyglutamine diseases inhibits aggregate formation, inhibits transglutaminase, inhibits caspase, or is neuroprotective.

18. The kit according to claim 17, wherein said compound useful for the treatment of polyglutamine diseases is selected from the group consisting of Congo red, cystamine, cysteamine, minocycline, ethyl eicosapentaenoate, and riluzole.

19. A method for decreasing neuronal polyglutamine containing aggregates, comprising administering at least one compound selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine, to a patient in need of such decrease.

20. A method for decreasing the amount of huntingtin protein in brain tissue, comprising administering at least one compound selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine, to a patient in need of such decrease.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

# *BIBDATASHEET*

Bib Data Sheet

**CONFIRMATION NO. 5654**

| SERIAL NUMBER | FILING DATE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 10/758,415 | 01/16/2004<br>RULE | 514 | 1614 | 2930-109 |

APPLICANTS

William S. Brusilow, Grosse Pointe, MI;

** CONTINUING DATA **********

This appln claims benefit of 60/440,627 01/17/2003

** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** SMALL ENTITY **
** 04/24/2004

| Foreign Priority claimed | STATE OR | SHEETS | TOTAL | INDEPENDENT |
|---|---|---|---|---|
| 35 USC 119 (a-d) conditions met | COUNTRY | DRAWING | CLAIMS | CLAIMS |
| Verified and Acknowledged | MI | 0 | 20 | 5 |

☐ yes ☐ no

☐ yes ☐ no ☐ Met after Allowance

Examiner's Signature Initials

ADDRESS
6449
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON , DC
20005

TITLE
Treatment of polyglutamine disorders caused by expanding genomic CAG nucleotides

| FILING FEE | FEES: Authority has been given in Paper | ☐ All Fees |
|---|---|---|
| RECEIVED 471 | No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following: | ☐ 1.16 Fees ( Filing )<br>☐ 1.17 Fees ( Processing Ext. of time )<br>☐ 1.18 Fees ( Issue ) |

| | |
|---|---|
| | ☐ Other _____ |
| | ☐ Credit |

# STIC SEARCH RESULTS FEEDBACK FORM

## Biotech-Chem Library

Questions about the scope or the results of the search? Contact ***the searcher or contact:***

**Mary Hale, Information Branch Supervisor**
**Remsen Bldg. 01 D86**
**571-272-2507**

## Voluntary Results Feedback Form

- *I am an examiner in Workgroup:* ☐ *Example: 1610*
- *Relevant prior art **found**, search results used as follows:*
  - ☐ 102 rejection
  - ☐ 103 rejection
  - ☐ Cited as being of interest.
  - ☐ Helped examiner better understand the invention.
  - ☐ Helped examiner better understand the state of the art in their technology.

*Types of relevant prior art found:*

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature
  (journal articles, conference proceedings, new product announcements etc.)

- *Relevant prior art **not found:***
  - ☐ Results verified the lack of relevant prior art (helped determine patentability).
  - ☐ Results were not useful in determining patentability or understanding the invention.

**Comments:**

**Drop off or send completed forms to STIC-Biotech-Chem Library Remsen Bldg.**

# National Library of Medicine - Medical Subject Headings

**2004 MeSH**

## MeSH Descriptor Data

Return to Entry Page

| | |
|---|---|
| **MeSH Heading** | Muscular Disorders, Atrophic |
| **Tree Number** | C05.651.534 |
| **Tree Number** | C10.668.491.175 |
| **Tree Number** | C10.668.550 |
| **Scope Note** | Disorders characterized by an abnormal reduction in muscle volume due to a decrease in the size or number of muscle fibers. Atrophy may result from diseases intrinsic to muscle tissue (e.g., MUSCULAR DYSTROPHY) or secondary to PERIPHERAL NERVOUS SYSTEM DISEASES that impair innervation to muscle tissue (e.g., MUSCULAR ATROPHY, SPINAL). |
| **Entry Term** | Atrophy, Disuse |
| **Entry Term** | Atrophy, Muscular, Spinobulbar |
| **Entry Term** | Atrophy, Spinopontine |
| **Entry Term** | Muscular Atrophy, Spinobulbar |
| **Entry Term** | Spinobulbar Muscular Atrophy |
| **Entry Term** | Atrophic Muscular Disorders |
| **Entry Term** | Spinobulbar Atrophy |
| **Entry Term** | Spinopontine Atrophy |
| **See Also** | Muscular Atrophy |
| **Allowable Qualifiers** | BL CF CI CL CN CO DH DI DT EC EH EM EN EP ET GE HI IM ME MI MO NU PA PC PP PS PX RA RH RI RT SU TH UR US VE VI |
| **Entry Version** | MUSCULAR DIS ATROPHIC |
| **Previous Indexing** | Muscular Atrophy (1966-1999) |
| **History Note** | 2000 |
| **Unique ID** | D020966 |

## MeSH Tree Structures

Musculoskeletal Diseases [C05]
- Muscular Diseases [C05.651]
  - Arthrogryposis [C05.651.102]
  - Compartment Syndromes [C05.651.180] +
  - Contracture [C05.651.197] +
  - Craniomandibular Disorders [C05.651.243] +
  - Eosinophilia-Myalgia Syndrome [C05.651.290]
  - Fatigue Syndrome, Chronic [C05.651.310]
  - Fibromyalgia [C05.651.324]
  - Isaacs Syndrome [C05.651.392]
  - Mitochondrial Myopathies [C05.651.460] +
  - Muscle Cramp [C05.651.475]
  - Muscle Neoplasms [C05.651.494]
  - Muscle Rigidity [C05.651.504]
  - Muscle Spasticity [C05.651.512]
  - Muscle Weakness [C05.651.515]
  - ▶ Muscular Disorders, Atrophic [C05.651.534]
    - Muscular Dystrophies [C05.651.534.500] +
    - Postpoliomyelitis Syndrome [C05.651.534.750]
  - Myofascial Pain Syndromes [C05.651.550] +
  - Myopathies, Structural, Congenital [C05.651.575] +
  - Myositis [C05.651.594] +
  - Myotonic Disorders [C05.651.662] +
  - Paralyses, Familial Periodic [C05.651.701] +
  - Polymyalgia Rheumatica [C05.651.742]
  - Rhabdomyolysis [C05.651.807] +
  - Tendinitis [C05.651.854]
  - Tenosynovitis [C05.651.884]

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Nervous System Diseases [C10]
- Neuromuscular Diseases [C10.668]
  - Muscular Diseases [C10.668.491]
    - ▶ Muscular Disorders, Atrophic [C10.668.491.175]
      - Muscular Dystrophies [C10.668.491.175.500] +
      - Postpoliomyelitis Syndrome [C10.668.491.175.750]
    - Eosinophilia-Myalgia Syndrome [C10.668.491.387]
    - Fibromyalgia [C10.668.491.425]
    - Mitochondrial Myopathies [C10.668.491.500] +
    - Myopathies, Structural, Congenital [C10.668.491.550] +
    - Myositis [C10.668.491.562] +

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=> fil reg; d ide l24 1-9
FILE 'REGISTRY' ENTERED AT 14:09:39 ON 28 SEP 2004
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   27 SEP 2004  HIGHEST RN 752974-11-1
DICTIONARY FILE UPDATES:  27 SEP 2004  HIGHEST RN 752974-11-1

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html



L24  ANSWER 1 OF 9  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   77182-82-2  REGISTRY
CN   Butanoic acid, 2-amino-4-(hydroxymethylphosphinyl)-, monoammonium salt
     (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Ammonium glufosinate
CN   Basta
CN   Basta Fl
CN   Basta LS
CN   Buster
CN   Dash
CN   Finale
CN   Finale 14SL
CN   Glufosinate monoammonium salt
CN   Glufosinate-ammonium
CN   HOE 00661
CN   HOE 39866
CN   Ignite
CN   Liberty
CN   Liberty (pesticide)
DR   82785-28-2, 106917-54-8, 118336-14-4
MF   C5 H12 N O4 P . H3 N
CI   COM
LC   STN Files:   AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS, CA, CABA,
       CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB,
       DIOGENES, HSDB*, MRCK*, MSDS-OHS, NIOSHTIC, PIRA, PROMT, RTECS*,
       SPECINFO, TOXCENTER, ULIDAT, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   EINECS**
         (**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA  CAplus document type:  Conference; Dissertation; Journal; Patent
RL.P   Roles from patents:  ANST (Analytical study); BIOL (Biological study);
       PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES
       (Uses)
RLD.P  Roles for non-specific derivatives from patents:  BIOL (Biological
       study); PROC (Process); USES (Uses)
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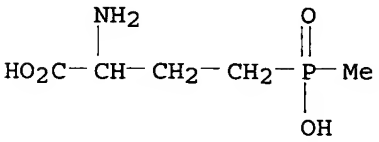
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)
CRN (51276-47-2)



● $NH_3$

357 REFERENCES IN FILE CA (1907 TO DATE)
42 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
358 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L24 ANSWER 2 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 59542-49-3 REGISTRY
CN Butanoic acid, 2-amino-4-(hydroxymethylphosphinyl)-, hydrochloride (9CI) (CA INDEX NAME)
OTHER NAMES:
CN DL-Phosphinothricin hydrochloride
CN **Glufosinate hydrochloride**
DR 58960-79-5
MF C5 H12 N O4 P . Cl H
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMINFORMRX, IFICDB, IFIPAT, IFIUDB, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: PREP (Preparation); PRP (Properties); RACT (Reactant or reagent)
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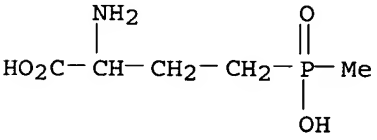
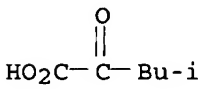


● HCl

14 REFERENCES IN FILE CA (1907 TO DATE)
14 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L24 ANSWER 3 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 51828-95-6 REGISTRY
CN Pentanoic acid, 4-methyl-2-oxo-, calcium salt (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **.alpha.-Ketoisocaproic acid calcium salt**
CN Calcium .alpha.-ketoisocaproate
CN Calcium .alpha.-oxoisocaproate

DR 95017-02-0, 196884-11-4
MF C6 H10 O3 . 1/2 Ca
CI COM
LC STN Files: BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, IFICDB, IFIPAT, IFIUDB, MSDS-OHS, TOXCENTER, USPATFULL
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation)
CRN (816-66-0)



1/2 Ca

20 REFERENCES IN FILE CA (1907 TO DATE)
20 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L24 ANSWER 4 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 51276-47-2 REGISTRY
CN Butanoic acid, 2-amino-4-(hydroxymethylphosphinyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (.+-.)-Phosphinothricin
CN 3-Amino-3-carboxypropylmethylphosphinic acid
CN DL-2-Amino-4-(methylphosphino)butanoic acid
CN DL-Phosphinothricin
CN **Glufosinate**
CN HOE 35956
FS 3D CONCORD
DR 126633-48-5, 53369-07-6
MF C5 H12 N O4 P
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, NIOSHTIC, PROMT, RTECS*, SPECINFO, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
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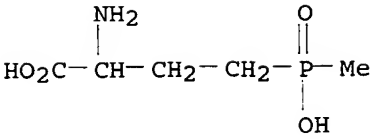

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

674 REFERENCES IN FILE CA (1907 TO DATE)
102 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
680 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L24 ANSWER 5 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN **21752-32-9** REGISTRY
CN Butanoic acid, 2-amino-4-[[S(S)]-S-methylsulfonimidoyl]-, (2S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Butanoic acid, 2-amino-4-(S-methylsulfonimidoyl)-, [S-(R*,R*)]-
CN Sulfoximine, S-(3-amino-3-carboxypropyl)-S-methyl-, (S)-L- (8CI)
OTHER NAMES:
CN L-Methionine-(S)-sulfoximine
FS STEREOSEARCH
DR 54631-79-7, 110202-65-8
MF C5 H12 N2 O3 S
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
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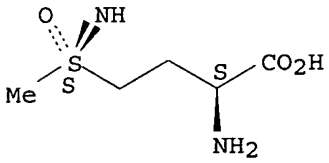
Absolute stereochemistry.



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

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2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
38 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L24 ANSWER 6 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 5072-23-1 REGISTRY
CN **Butanoic acid, 2-amino-4-(S-ethylsulfonimidoyl)- (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Sulfoximine, 3-amino-3-carboxypropyl ethyl (6CI)
CN Sulfoximine, S-(3-amino-3-carboxypropyl)-S-ethyl- (7CI, 8CI)

FS 3D CONCORD
DR 82731-15-5
MF C6 H14 N2 O3 S
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, TOXCENTER
(*File contains numerically searchable property data)
DT.CA CAplus document type: Journal; Patent
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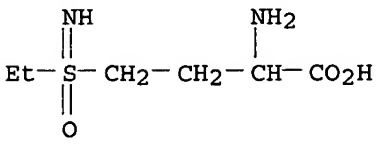
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); NORL (No role in record)



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L24 ANSWER 7 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 1821-02-9 REGISTRY
CN Pentanoic acid, 2-oxo- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Valeric acid, 2-oxo- (6CI, 7CI, 8CI)
OTHER NAMES:
CN **.alpha.-keto-Valeric acid**
CN .alpha.-Ketovaleric acid
CN .alpha.-Oxo-n-valeric acid
CN .alpha.-Oxopentanoic acid
CN .alpha.-Oxovaleric acid
CN 2-Ketopentanoic acid
CN 2-Ketovaleric acid
CN 2-Oxo-n-valeric acid
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FS 3D CONCORD
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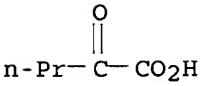
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, EMBASE, HODOC*, IFICDB, IFIPAT, IFIUDB, MEDLINE, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical

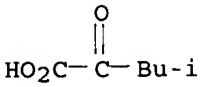
study)



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

401 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
401 REFERENCES IN FILE CAPLUS (1907 TO DATE)
25 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

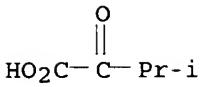
L24 ANSWER 8 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 816-66-0 REGISTRY
CN Pentanoic acid, 4-methyl-2-oxo- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Valeric acid, 4-methyl-2-oxo- (8CI)
OTHER NAMES:
CN **.alpha.-Ketoisocaproic acid**
CN .alpha.-Ketoisocapronic acid
CN .alpha.-Oxoisocaproic acid
CN 2-keto-4-Methylvaleric acid
CN 2-Ketoisocaproic acid
CN 2-Oxo-4-methylpentanoic acid
CN 2-Oxo-4-methylvaleric acid
CN 2-Oxoisocaproic acid
CN 2-Oxoleucine
CN 4-Methyl-2-oxopentanoic acid
CN 4-Methyl-2-oxovaleric acid
CN Ketoleucine
FS 3D CONCORD
MF C6 H10 O3
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, NAPRALERT, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties)



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1487 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1488 REFERENCES IN FILE CAPLUS (1907 TO DATE)
14 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L24 ANSWER 9 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 759-05-7 REGISTRY
CN Butanoic acid, 3-methyl-2-oxo- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Butyric acid, 3-methyl-2-oxo- (8CI)
OTHER NAMES:
CN **.alpha.-keto-.beta.-Methylbutyric acid**
CN .alpha.-keto-Isovaleric acid
CN .alpha.-Ketoisovaleric acid
CN .alpha.-Oxo-.beta.-methylbutyric acid
CN .alpha.-Oxoisovaleric acid
CN 2-keto-3-Methylbutyric acid
CN 2-Ketoisovaleric acid
CN 2-Oxo-3-methylbutanoic acid
CN 2-Oxo-3-methylbutyric acid
CN 2-Oxoisovaleric acid
CN 3-Methyl-2-oxobutanoic acid
CN 3-Methyl-2-oxobutyrate
CN 3-Methyl-2-oxobutyric acid
CN Dimethylpyruvic acid
CN Isopropylglyoxylic acid
CN Ketovaline
FS 3D CONCORD
MF C5 H8 O3
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, EMBASE, HODOC*, IFICDB, IFIPAT, IFIUDB, MEDLINE, NAPRALERT, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); PRP (Properties); RACT (Reactant or reagent)



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

969 REFERENCES IN FILE CA (1907 TO DATE)
9 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
971 REFERENCES IN FILE CAPLUS (1907 TO DATE)
30 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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=> fil pascal jic esbio biotechds confsci wpids
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=> d que l119
L59        1478 SEA KETOVALINE OR KETOISOVALER? OR KETOLEUCINE OR KETOISOCAPRO?
                 OR KETOVALER? OR OXOPENTANO? OR PHOSPHINOTHRICIN#
L60          46 SEA HOE(W)(00661 OR 35956 OR 39866) OR HOE00661 OR HOE35956 OR
                HOE39866
L61         516 SEA ALPHA KETO(1W) ACID#
L62        1857 SEA (METHIONINE OR ETHIONINE)(1W) SULFOXIMINE OR GLUFOSINAT#
L63          15 SEA (ALPHA KETO)(W)(ISOCAPRO? OR (BETA(W)(METHYLBUTYR? OR
                METHYL BUTYR?)) OR BETAMETHYLBUTYR? OR VALER?)
L64         383 SEA ALPHA(W)(KETOISOCAPRO? OR KETOVALER?)
L115       1742 SEA POLYGLUTAMINE OR POLY GLUTAMINE
L116      17046 SEA HUNTINGTON? OR SPINOCEREBELLAR(W)(ATAXIA# OR DEGENERAT?)
                OR SPINOBULBAR(2A) MUSC?(2A) ATROPH?
L117      15600 SEA MUSCULAR DYSTROPH? OR POSTPOLIO? OR POST POLIO?
L118       4980 SEA (L59 OR L60 OR L61 OR L62 OR L63 OR L64)
L119          5 SEA (L115 OR L116 OR L117) AND L118


=> fil uspatf; d que l109;d que l114
FILE 'USPATFULL' ENTERED AT 15:27:32 ON 28 SEP 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 28 Sep 2004 (20040928/PD)
FILE LAST UPDATED: 28 Sep 2004 (20040928/ED)
HIGHEST GRANTED PATENT NUMBER: US6799328
HIGHEST APPLICATION PUBLICATION NUMBER: US2004187181
CA INDEXING IS CURRENT THROUGH 28 Sep 2004 (20040928/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 28 Sep 2004 (20040928/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2004

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
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>>> are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc.                                                        <<<

>>> USPATFULL and USPAT2 can be accessed and searched together        <<<
>>> through the new cluster USPATALL.  Type FILE USPATALL to          <<<
>>> enter this cluster.                                              <<<
>>>                                                                  <<<
>>> Use USPATALL when searching terms such as patent assignees,      <<<
>>> classifications, or claims, that may potentially change from     <<<
>>> the earliest to the latest publication.                          <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.


L4            1 SEA FILE=REGISTRY ABB=ON  21752-32-9
L5            3 SEA FILE=REGISTRY ABB=ON  (GLUFOSINATE/CN OR "GLUFOSINATE
                HYDROCHLORIDE"/CN OR "GLUFOSINATE MONOAMMONIUM SALT"/CN) OR
                GLUFOSINATE-AMMONIUM/CN
L6            1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-VALERIC ACID"/CN
L7            1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-.BETA.-METHYLBUTYRIC
                ACID"/CN
L17           1 SEA FILE=REGISTRY ABB=ON  "BUTANOIC ACID, 2-AMINO-4-(S-ETHYLSUL
                FONIMIDOYL)-"/CN
L19           2 SEA FILE=REGISTRY ABB=ON  .ALPHA.-KETOISOCAPROIC ACID?/CN
L21           2 SEA FILE=REGISTRY ABB=ON  POLYGLUTAMINE/CN
L24           9 SEA FILE=REGISTRY ABB=ON  (L4 OR L5 OR L6 OR L7) OR L17 OR L19

L106        424 SEA FILE=USPATFULL ABB=ON  L24
L107         86 SEA FILE=USPATFULL ABB=ON  L21 OR (POLYGLUTAMINE OR POLY
                GLUTAMINE)/IT
L108       2369 SEA FILE=USPATFULL ABB=ON  (HUNTINGTON? OR SPINOCEREBELLAR
                ATAXIA# OR SPINOBULBAR(2A)MUSC?(2A)ATROPH? OR MUSCULAR
                DYSTROPH? OR POSTPOLIO?)/IT,TI,AB,CLM
L109          1 SEA FILE=USPATFULL ABB=ON  L106 AND (L107 OR L108)



L21           2 SEA FILE=REGISTRY ABB=ON  POLYGLUTAMINE/CN
L107         86 SEA FILE=USPATFULL ABB=ON  L21 OR (POLYGLUTAMINE OR POLY
                GLUTAMINE)/IT
L108       2369 SEA FILE=USPATFULL ABB=ON  (HUNTINGTON? OR SPINOCEREBELLAR
                ATAXIA# OR SPINOBULBAR(2A)MUSC?(2A)ATROPH? OR MUSCULAR
                DYSTROPH? OR POSTPOLIO?)/IT,TI,AB,CLM
L111        564 SEA FILE=USPATFULL ABB=ON  (KETOVALINE/IT OR KETOISOVALER?/IT
                OR KETOLEUCINE/IT OR KETOISOCAPRO?/IT OR KETOVALER?/IT OR
                OXOPENTANO?/IT OR PHOSPHINOTHRICIN#/IT)
L112        318 SEA FILE=USPATFULL ABB=ON  (HOE/IT(W)(00661/IT OR 35956/IT OR
                39866/IT) OR HOE00661/IT OR HOE35956/IT OR HOE39866/IT) OR
                (ALPHA KETO/IT(1W) ACID#/IT) OR ((METHIONINE/IT OR ETHIONINE/IT
                )(1W) SULFOXIMINE/IT OR GLUFOSINAT#/IT) OR ((ALPHA KETO/IT)(W)(
                ISOCAPRO?/IT OR (BETA/IT(W)(METHYLBUTYR?/IT OR METHYL BUTYR?/IT
                )) OR BETAMETHYLBUTYR?/IT OR VALER?/IT) ) OR (ALPHA/IT(W)(KETOI
                SOCAPRO?/IT OR KETOVALER?/IT) )
L114          5 SEA FILE=USPATFULL ABB=ON  (L111 OR L112) AND (L107 OR L108)


=> s l109 or l114
L120          5 L109 OR L114

=> fil embase; d que l105
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FILE 'EMBASE' ENTERED AT 15:27:48 ON 28 SEP 2004
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 FILE COVERS 1974 TO 24 Sep 2004 (20040924/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

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L4             1 SEA FILE=REGISTRY ABB=ON  21752-32-9
L5             3 SEA FILE=REGISTRY ABB=ON  (GLUFOSINATE/CN OR "GLUFOSINATE
                 HYDROCHLORIDE"/CN OR "GLUFOSINATE MONOAMMONIUM SALT"/CN) OR
                 GLUFOSINATE-AMMONIUM/CN
L6             1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-VALERIC ACID"/CN
L7             1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-.BETA.-METHYLBUTYRIC
                 ACID"/CN
L17            1 SEA FILE=REGISTRY ABB=ON  "BUTANOIC ACID, 2-AMINO-4-(S-ETHYLSUL
                 FONIMIDOYL)-"/CN
L19            2 SEA FILE=REGISTRY ABB=ON  .ALPHA.-KETOISOCAPROIC ACID?/CN
L24            9 SEA FILE=REGISTRY ABB=ON  (L4 OR L5 OR L6 OR L7) OR L17 OR L19

L94          671 SEA FILE=EMBASE ABB=ON  L24
L95          706 SEA FILE=EMBASE ABB=ON  POLYGLUTAMINE/CT
L96         6173 SEA FILE=EMBASE ABB=ON  HUNTINGTON CHOREA/CT
L97           60 SEA FILE=EMBASE ABB=ON  SPINOCEREBELLAR ATAXIA/CT OR SPINOCEREB
                 ELLAR ATAXIA 2/CT OR SPINOCEREBELLAR ATAXIA TYPE 1/CT OR
                 SPINOCEREBELLAR ATAXIA TYPE 10/CT
L98           10 SEA FILE=EMBASE ABB=ON  SPINOCEREBELLAR ATAXIA TYPE 12/CT OR
                 SPINOCEREBELLAR ATAXIA TYPE 14/CT OR SPINOCEREBELLAR ATAXIA
                 TYPE 17/CT OR SPINOCEREBELLAR ATAXIA TYPE 2/CT
L99            6 SEA FILE=EMBASE ABB=ON  SPINOCEREBELLAR ATAXIA TYPE 20/CT OR
                 SPINOCEREBELLAR ATAXIA TYPE 3/CT OR SPINOCEREBELLAR ATAXIA
                 TYPE 4/CT OR SPINOCEREBELLAR ATAXIA TYPE 5/CT
L100           7 SEA FILE=EMBASE ABB=ON  SPINOCEREBELLAR ATAXIA TYPE 6/CT OR
                 SPINOCEREBELLAR ATAXIA TYPE 7/CT OR SPINOCEREBELLAR ATAXIA
                 TYPE 8/CT
L101        1385 SEA FILE=EMBASE ABB=ON  SPINOCEREBELLAR DEGENERATION/CT OR
                 SPINOCEREBELLAR DEGENERATION TYPE 6/CT OR SPINOCEREBELLAR
                 DEGENERATION TYPE 7/CT
L102         172 SEA FILE=EMBASE ABB=ON  KENNEDY DISEASE/CT
L103       13783 SEA FILE=EMBASE ABB=ON  MUSCULAR DYSTROPHY+NT/CT
L104         333 SEA FILE=EMBASE ABB=ON  POSTPOLIOMYELITIS SYNDROME/CT
L105           3 SEA FILE=EMBASE ABB=ON  L94 AND (L95 OR L96 OR L97 OR L98 OR
                 L99 OR L100 OR L101 OR L102 OR L103 OR L104)


=> fil medl; d que l74; d que l76; d que l79
FILE 'MEDLINE' ENTERED AT 15:28:01 ON 28 SEP 2004

 FILE LAST UPDATED: 25 SEP 2004 (20040925/UP). FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
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substance identification.

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L4              1 SEA FILE=REGISTRY ABB=ON  21752-32-9
L5              3 SEA FILE=REGISTRY ABB=ON  (GLUFOSINATE/CN OR "GLUFOSINATE
                  HYDROCHLORIDE"/CN OR "GLUFOSINATE MONOAMMONIUM SALT"/CN) OR
                  GLUFOSINATE-AMMONIUM/CN
L6              1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-VALERIC ACID"/CN
L7              1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-.BETA.-METHYLBUTYRIC
                  ACID"/CN
L17             1 SEA FILE=REGISTRY ABB=ON  "BUTANOIC ACID, 2-AMINO-4-(S-ETHYLSUL
                  FONIMIDOYL)-"/CN
L19             2 SEA FILE=REGISTRY ABB=ON  .ALPHA.-KETOISOCAPROIC ACID?/CN
L24             9 SEA FILE=REGISTRY ABB=ON  (L4 OR L5 OR L6 OR L7) OR L17 OR L19

L67           760 SEA FILE=MEDLINE ABB=ON  L24
L70          5474 SEA FILE=MEDLINE ABB=ON  HUNTINGTON DISEASE/CT
L71          3608 SEA FILE=MEDLINE ABB=ON  SPINOCEREBELLAR DEGENERATIONS+NT/CT
L72         14324 SEA FILE=MEDLINE ABB=ON  MUSCULAR DISORDERS, ATROPHIC+NT/CT
L74             3 SEA FILE=MEDLINE ABB=ON  L67 AND (L70 OR L71 OR L72)



L68         31078 SEA FILE=MEDLINE ABB=ON  KETO ACIDS+NT/CT
L70          5474 SEA FILE=MEDLINE ABB=ON  HUNTINGTON DISEASE/CT
L71          3608 SEA FILE=MEDLINE ABB=ON  SPINOCEREBELLAR DEGENERATIONS+NT/CT
L72         14324 SEA FILE=MEDLINE ABB=ON  MUSCULAR DISORDERS, ATROPHIC+NT/CT
L75          5648 SEA FILE=MEDLINE ABB=ON  L68(L)(TU OR AD OR PD OR PK)/CT
L76             6 SEA FILE=MEDLINE ABB=ON  L75 AND (L70 OR L71 OR L72)



L4              1 SEA FILE=REGISTRY ABB=ON  21752-32-9
L5              3 SEA FILE=REGISTRY ABB=ON  (GLUFOSINATE/CN OR "GLUFOSINATE
                  HYDROCHLORIDE"/CN OR "GLUFOSINATE MONOAMMONIUM SALT"/CN) OR
                  GLUFOSINATE-AMMONIUM/CN
L6              1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-VALERIC ACID"/CN
L7              1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-.BETA.-METHYLBUTYRIC
                  ACID"/CN
L17             1 SEA FILE=REGISTRY ABB=ON  "BUTANOIC ACID, 2-AMINO-4-(S-ETHYLSUL
                  FONIMIDOYL)-"/CN
L19             2 SEA FILE=REGISTRY ABB=ON  .ALPHA.-KETOISOCAPROIC ACID?/CN
L21             2 SEA FILE=REGISTRY ABB=ON  POLYGLUTAMINE/CN
L24             9 SEA FILE=REGISTRY ABB=ON  (L4 OR L5 OR L6 OR L7) OR L17 OR L19

L67           760 SEA FILE=MEDLINE ABB=ON  L24
L68         31078 SEA FILE=MEDLINE ABB=ON  KETO ACIDS+NT/CT
L75          5648 SEA FILE=MEDLINE ABB=ON  L68(L)(TU OR AD OR PD OR PK)/CT
L78          1100 SEA FILE=MEDLINE ABB=ON  L21
L79             0 SEA FILE=MEDLINE ABB=ON  L78 AND (L67 OR L75)


=> s l74 or l76
L121            8 L74 OR L76

=> fil drugu biotechno caba ipa; d que l86; fil agricola biosis toxcenter; d que l84; fil
capl; d que l40; d que l84; s l40 or l82
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L5             3 SEA FILE=REGISTRY ABB=ON  (GLUFOSINATE/CN OR "GLUFOSINATE
                 HYDROCHLORIDE"/CN OR "GLUFOSINATE MONOAMMONIUM SALT"/CN) OR
                 GLUFOSINATE-AMMONIUM/CN
L6             1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-VALERIC ACID"/CN
L7             1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-.BETA.-METHYLBUTYRIC
                 ACID"/CN
L17            1 SEA FILE=REGISTRY ABB=ON  "BUTANOIC ACID, 2-AMINO-4-(S-ETHYLSUL
                 FONIMIDOYL)-"/CN
L19            2 SEA FILE=REGISTRY ABB=ON  .ALPHA.-KETOISOCAPROIC ACID?/CN
L24            9 SEA FILE=REGISTRY ABB=ON  (L4 OR L5 OR L6 OR L7) OR L17 OR L19

L58         1420 SEA L24
L59         1478 SEA KETOVALINE OR KETOISOVALER? OR KETOLEUCINE OR KETOISOCAPRO?
                  OR KETOVALER? OR OXOPENTANO? OR PHOSPHINOTHRICIN#
L60           46 SEA HOE(W)(00661 OR 35956 OR 39866) OR HOE00661 OR HOE35956 OR
                 HOE39866
L61          516 SEA ALPHA KETO(1W) ACID#
L62         1857 SEA (METHIONINE OR ETHIONINE)(1W) SULFOXIMINE OR GLUFOSINAT#
L63           15 SEA (ALPHA KETO)(W)(ISOCAPRO? OR (BETA(W)(METHYLBUTYR? OR
                 METHYL BUTYR?)) OR BETAMETHYLBUTYR? OR VALER?)
L64          383 SEA ALPHA(W)(KETOISOCAPRO? OR KETOVALER?)
L65         2620 SEA HUNTINGTON? OR SPINOCEREBELLAR(2A) ATAXI? OR (SPINOBULBAR
                 OR SPINO BULBAR)(2A) ATROPH?(2A) MUSC?
L85         4828 SEA MUSCULAR DYSTROPH? OR POSTPOLIO?
L86            0 SEA (L58 OR L59 OR L60 OR L61 OR L62 OR L63 OR L64) AND (L65
                 OR L85)


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L5             3 SEA FILE=REGISTRY ABB=ON  (GLUFOSINATE/CN OR "GLUFOSINATE
                 HYDROCHLORIDE"/CN OR "GLUFOSINATE MONOAMMONIUM SALT"/CN) OR
                 GLUFOSINATE-AMMONIUM/CN
L6             1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-VALERIC ACID"/CN
L7             1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-.BETA.-METHYLBUTYRIC
                 ACID"/CN
L17            1 SEA FILE=REGISTRY ABB=ON  "BUTANOIC ACID, 2-AMINO-4-(S-ETHYLSUL
                 FONIMIDOYL)-"/CN
L19            2 SEA FILE=REGISTRY ABB=ON  .ALPHA.-KETOISOCAPROIC ACID?/CN
L24            9 SEA FILE=REGISTRY ABB=ON  (L4 OR L5 OR L6 OR L7) OR L17 OR L19

L52         2333 SEA L24
L53         3108 SEA KETOVALINE OR KETOISOVALER? OR KETOLEUCINE OR KETOISOCAPRO?
                  OR KETOVALER? OR OXOPENTANO? OR PHOSPHINOTHRICIN#
```

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L54          48 SEA HOE(W)(00661 OR 35956 OR 39866) OR HOE00661 OR HOE35956 OR
                HOE39866
L55        2628 SEA POLYGLUTAMINE OR POLY GLUTAMINE
L56       13427 SEA HUNTINGTON? OR SPINOCEREBELLAR(2A) ATAXI? OR (SPINOBULBAR
                OR SPINO BULBAR)(2A) ATROPH?(2A) MUSC?
L83       14503 SEA MUSCULAR DYSTROPH? OR POSTPOLIO?
L84           4 SEA (L52 OR L53 OR L54) AND (L55 OR L56 OR L83)


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FILE COVERS 1907 - 28 Sep 2004  VOL 141 ISS 14
FILE LAST UPDATED: 27 Sep 2004  (20040927/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L4            1 SEA FILE=REGISTRY ABB=ON  21752-32-9
L5            3 SEA FILE=REGISTRY ABB=ON  (GLUFOSINATE/CN OR "GLUFOSINATE
                HYDROCHLORIDE"/CN OR "GLUFOSINATE MONOAMMONIUM SALT"/CN) OR
                GLUFOSINATE-AMMONIUM/CN
L6            1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-VALERIC ACID"/CN
L7            1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-.BETA.-METHYLBUTYRIC
                ACID"/CN
L17           1 SEA FILE=REGISTRY ABB=ON  "BUTANOIC ACID, 2-AMINO-4-(S-ETHYLSUL
                FONIMIDOYL)-"/CN
L19           2 SEA FILE=REGISTRY ABB=ON  .ALPHA.-KETOISOCAPROIC ACID?/CN
L20           6 SEA FILE=REGISTRY ABB=ON  LEUCINE/CN OR ISOLEUCINE/CN OR
                VALINE/CN
L21           2 SEA FILE=REGISTRY ABB=ON  POLYGLUTAMINE/CN
L24           9 SEA FILE=REGISTRY ABB=ON  (L4 OR L5 OR L6 OR L7) OR L17 OR L19

L25        3108 SEA FILE=CAPLUS ABB=ON  L24
L28         721 SEA FILE=CAPLUS ABB=ON  L21
L29         366 SEA FILE=CAPLUS ABB=ON  L28(L)ADV/RL
L31        4030 SEA FILE=CAPLUS ABB=ON  HUNTINGTON?/OBI
L32         641 SEA FILE=CAPLUS ABB=ON  ATAXIA#/OBI(L)SPINOCEREBELLAR/OBI
L33          29 SEA FILE=CAPLUS ABB=ON  SPINOBULBAR/OBI(L)ATROPH?/OBI(L)MUSC?/O
                BI
L37       44805 SEA FILE=CAPLUS ABB=ON  L20
L39        2388 SEA FILE=CAPLUS ABB=ON  (L25 OR L37)(L)(THU OR BAC OR PAC OR
                PKT OR DMA)/RL
L40           8 SEA FILE=CAPLUS ABB=ON  L39 AND (L29 OR (L31 OR L32 OR L33))
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L4              1 SEA FILE=REGISTRY ABB=ON  21752-32-9
L5              3 SEA FILE=REGISTRY ABB=ON  (GLUFOSINATE/CN OR "GLUFOSINATE
                  HYDROCHLORIDE"/CN OR "GLUFOSINATE MONOAMMONIUM SALT"/CN) OR
                  GLUFOSINATE-AMMONIUM/CN
L6              1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-VALERIC ACID"/CN
L7              1 SEA FILE=REGISTRY ABB=ON  ".ALPHA.-KETO-.BETA.-METHYLBUTYRIC
                  ACID"/CN
L17             1 SEA FILE=REGISTRY ABB=ON  "BUTANOIC ACID, 2-AMINO-4-(S-ETHYLSUL
                  FONIMIDOYL)-"/CN
L19             2 SEA FILE=REGISTRY ABB=ON  .ALPHA.-KETOISOCAPROIC ACID?/CN
L24             9 SEA FILE=REGISTRY ABB=ON  (L4 OR L5 OR L6 OR L7) OR L17 OR L19

L52          2333 SEA L24
L53          3108 SEA KETOVALINE OR KETOISOVALER? OR KETOLEUCINE OR KETOISOCAPRO?
                   OR KETOVALER? OR OXOPENTANO? OR PHOSPHINOTHRICIN#
L54            48 SEA HOE(W)(00661 OR 35956 OR 39866) OR HOE00661 OR HOE35956 OR
                  HOE39866
L55          2628 SEA POLYGLUTAMINE OR POLY GLUTAMINE
L56         13427 SEA HUNTINGTON? OR SPINOCEREBELLAR(2A) ATAXI? OR (SPINOBULBAR
                  OR SPINO BULBAR)(2A) ATROPH?(2A) MUSC?
L83         14503 SEA MUSCULAR DYSTROPH? OR POSTPOLIO?
L84             4 SEA (L52 OR L53 OR L54) AND (L55 OR L56 OR L83)



L122           10 L40 OR L82


=> dup rem l121,l122,l119,l105,l84,l120
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PROCESSING COMPLETED FOR L121
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PROCESSING COMPLETED FOR L122
PROCESSING COMPLETED FOR L119
PROCESSING COMPLETED FOR L105
PROCESSING COMPLETED FOR L84
PROCESSING COMPLETED FOR L120
L124 29 DUP REM L121 L122 L119 L105 L84 L120 (6 DUPLICATES REMOVED)
ANSWERS '1-8' FROM FILE MEDLINE
ANSWERS '9-18' FROM FILE CAPLUS
ANSWERS '19-20' FROM FILE PASCAL
ANSWER '21' FROM FILE WPIDS
ANSWERS '22-23' FROM FILE EMBASE
ANSWERS '24-25' FROM FILE BIOSIS
ANSWERS '26-29' FROM FILE USPATFULL

=> d iall 1-8; d ibib ed ab hitrn 9-18; d iall 19-25; d ibib ab hitrn 26-29

L124 ANSWER 1 OF 29 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 84083046 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6360490
TITLE: Therapeutic aspects of branched-chain amino and keto acids.
AUTHOR: Walser M
SOURCE: Clinical science (London, England : 1979), (1984 Jan) 66 (1) 1-15. Ref: 173
Journal code: 7905731. ISSN: 0143-5221.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198402
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 20000303
Entered Medline: 19840224
CONTROLLED TERM: Check Tags: Human
Amino Acids, Branched-Chain: ME, metabolism
*Amino Acids, Branched-Chain: TU, therapeutic use
Animals
Brain: ME, metabolism
Chickens
Dogs
Hepatic Encephalopathy: DT, drug therapy
Intestinal Absorption
Keto Acids: ME, metabolism
***Keto Acids: TU, therapeutic use**
Kidney Failure, Chronic: DT, drug therapy
Leucine: ME, metabolism
Leucine: TU, therapeutic use
Liver: ME, metabolism
**Muscular Dystrophies: DT, drug therapy**
Proteins: ME, metabolism
Rats
Swine
CAS REGISTRY NO.: 61-90-5 (Leucine)
CHEMICAL NAME: 0 (Amino Acids, Branched-Chain); 0 (Keto Acids); 0 (Proteins)

L124 ANSWER 2 OF 29 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 82219800 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7088016
TITLE: Branched-chain ketoacids reduce muscle protein degradation in Duchenne muscular dystrophy.
AUTHOR: Stewart P M; Walser M; Drachman D B

CONTRACT NUMBER: AM-18020 (NIADDK)
RR-00052 (NCRR)
RR35-20 (NCRR)
SOURCE: Muscle & nerve, (1982 Mar) 5 (3) 197-201.
Journal code: 7803146. ISSN: 0148-639X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198208
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 20000303
Entered Medline: 19820807

ABSTRACT:
In order to determine whether branched-chain ketoacids can reduce the excessive rate of muscle protein degradation that characterizes Duchenne muscular dystrophy, nine boys affected with the disease were studied in a metabolic ward while receiving meat-free diets. After a three-day equilibration period, excretion rates of 3-methylhistidine and creatinine were measured in two consecutive four-day periods. In the second period, a supplement containing a mixture of ornithine alpha-ketoisocaproate, alpha-ketoisovalerate, and alpha-keto-beta-methylvalerate in a proportion of 4:1:1 was administered orally at a dosage of 0.45 gm/kg/day. During treatment with the ketoacids, 3-methylhistidine excretion fell by a small (mean: 14%) but highly significant (P less than 0.01) extent, whether expressed in absolute terms or in relation to creatinine excretion. No adverse effects were noted. We conclude that this mixture of ketoacids acutely reduces muscle protein degradation in patients with Duchenne muscular dystrophy.

CONTROLLED TERM: Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Child
Child, Preschool
Creatinine: UR, urine
***Keto Acids: TU, therapeutic use**
Methylhistidines: UR, urine
*Muscle Proteins: ME, metabolism
***Muscular Dystrophies: DT, drug therapy**
**Muscular Dystrophies: ME, metabolism**
Nitrogen: UR, urine
CAS REGISTRY NO.: 60-27-5 (Creatinine); 7727-37-9 (Nitrogen)
CHEMICAL NAME: 0 (Keto Acids); 0 (Methylhistidines); 0 (Muscle Proteins)

L124 ANSWER 3 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2004185771 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15081596
TITLE: Blockade of quinolinic acid-induced neurotoxicity by pyruvate is associated with inhibition of glial activation in a model of Huntington's disease.
AUTHOR: Ryu Jae K; Kim Seung U; McLarnon James G
CORPORATE SOURCE: Department of Pharmacology and Therapeutics, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada V6T 1Z3.
SOURCE: Experimental neurology, (2004 May) 187 (1) 150-9.
Journal code: 0370712. ISSN: 0014-4886.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20040415
Last Updated on STN: 20040511
Entered Medline: 20040510

ABSTRACT:
In this study, we have examined the mechanisms involved in pyruvate-mediated neuroprotection against quinolinic acid (QA)-induced striatal damage. QA injection into the striatum caused widespread neuronal damage and extensive areas of lesions in core and penumbra. The involvement of oxidative-mediated striatal damage was suggested by increased expressions of peroxynitrite, marked lipid peroxidation, and formation of DNA oxidative damage products. Administration of pyruvate, a glycolysis end product with antioxidant activity, significantly reduced QA-mediated striatal lesions, neuronal degeneration, and oxidative damage, whereas another energy substrate, lactate, was ineffective against oxidative damage and only partially effective in reducing lesions and neuronal degeneration. Treatment with the iNOS inhibitor aminoguanidine attenuated QA-mediated striatal lesions and reduced oxidative damage, indicating that iNOS activation may be involved in the striatal oxidative damage induced by QA. A role for glial cells in mediating oxidative damage was suggested because pyruvate blocked the expression of iNOS and nitrotyrosine in activated microglia and astrocytes in QA-injected striatum. These data suggest that pyruvate reduces oxidative free radical damage in QA-injected striatum and could have clinical utility in the treatment of Huntington's disease (HD).

CONTROLLED TERM: Check Tags: Male; Support, Non-U.S. Gov't
Animals
Disease Models, Animal
Drug Administration Routes
Enzyme Inhibitors: PD, pharmacology
Guanidines: PD, pharmacology
**Huntington Disease: CI, chemically induced**
***Huntington Disease: ME, metabolism**
**Huntington Disease: PA, pathology**
Lactic Acid: PD, pharmacology
Neostriatum: DE, drug effects
*Neostriatum: ME, metabolism
Neostriatum: PA, pathology
Neuroglia: DE, drug effects
*Neuroglia: ME, metabolism
Neuroglia: PA, pathology
*Neuroprotective Agents: PD, pharmacology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Oxidative Stress: DE, drug effects
***Pyruvic Acid: PD, pharmacology**
*Quinolinic Acid: AI, antagonists & inhibitors
Quinolinic Acid: TO, toxicity
Rats
Rats, Sprague-Dawley
Stereotaxic Techniques
*Tyrosine: AA, analogs & derivatives
Tyrosine: BI, biosynthesis

CAS REGISTRY NO.: 127-17-3 (Pyruvic Acid); 3604-79-3 (3-nitrotyrosine); 50-21-5 (Lactic Acid); 55520-40-6 (Tyrosine); 79-17-4 (pimagedine); 89-00-9 (Quinolinic Acid)

CHEMICAL NAME: 0 (Enzyme Inhibitors); 0 (Guanidines); 0 (Neuroprotective Agents); EC 1.14.13.- (inducible nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase)

L124 ANSWER 4 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2003477331 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14552912
TITLE: Neuroprotective effects of pyruvate in the quinolinic acid rat model of Huntington's disease.
AUTHOR: Ryu Jae K; Kim Seung U; McLarnon James G
CORPORATE SOURCE: Department of Pharmacology and Therapeutics, Faculty of Medicine, The University of British Columbia, V6T 1Z3, Vancouver, BC, Canada.

SOURCE: Experimental neurology, (2003 Oct) 183 (2) 700-4.
Journal code: 0370712. ISSN: 0014-4886.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20031015
Last Updated on STN: 20031101
Entered Medline: 20031031

ABSTRACT:
The neuroprotective effects of pyruvate, the end metabolite of glycolysis, were studied in an animal model of Huntington's disease (HD). Intrastriatal injection of quinolinic acid (QA) caused widespread damage to rat striatum as determined from cresyl violet staining and immunohistochemical analysis. Intraperitoneal administration of pyruvate at doses of 500-1000 mg/kg significantly reduced striatal lesions induced by QA. A lower pyruvate concentration of 250 mg/kg was not protective; however, quadruple applications at this dosage was effective in reducing lesion volumes. The protective effects of pyruvate were found over a range of times, from application at the time of QA injection to 1 h post-administration; however, no protection was conferred if pyruvate was applied 30 min prior to QA injection or 3 h post-administration. We also found pyruvate protects different types of striatal neurons against QA toxicity including GABAergic projection neurons, cholinergic interneurons and NADPH-diaphorase interneurons. These results suggest that pyruvate may be effective in reducing neuronal damage in HD.

CONTROLLED TERM: Check Tags: Male; Support, Non-U.S. Gov't
Animals
Corpus Striatum: DE, drug effects
Corpus Striatum: PA, pathology
Disease Models, Animal
Dose-Response Relationship, Drug
Drug Administration Routes
**Huntington Disease: CI, chemically induced**
***Huntington Disease: DT, drug therapy**
**Huntington Disease: PA, pathology**
Interneurons: DE, drug effects
Interneurons: PA, pathology
Neurons: DE, drug effects
Neurons: PA, pathology
*Neuroprotective Agents: TU, therapeutic use
***Pyruvic Acid: TU, therapeutic use**
*Quinolinic Acid
Rats
Rats, Sprague-Dawley
Time Factors
Treatment Outcome
CAS REGISTRY NO.: 127-17-3 (Pyruvic Acid); 89-00-9 (Quinolinic Acid)
CHEMICAL NAME: 0 (Neuroprotective Agents)

L124 ANSWER 5 OF 29 MEDLINE on STN

ACCESSION NUMBER: 1999138689 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9949201
TITLE: The Friedreich's ataxia mutation confers cellular sensitivity to oxidant stress which is rescued by chelators of iron and calcium and inhibitors of apoptosis.
AUTHOR: Wong A; Yang J; Cavadini P; Gellera C; Lonnerdal B; Taroni F; Cortopassi G
CORPORATE SOURCE: Department of Molecular Biosciences, 1311 Haring Hall, University of California, Davis, CA 95616, USA.
CONTRACT NUMBER: AG 11967 (NIA)
SOURCE: Human molecular genetics, (1999 Mar) 8 (3) 425-30.

Journal code: 9208958. ISSN: 0964-6906.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990517
Last Updated on STN: 20000303
Entered Medline: 19990503

ABSTRACT:
Expansions of an intronic GAA repeat reduce the expression of frataxin and cause Friedreich's ataxia (FRDA), an autosomal recessive neurodegenerative disease. Frataxin is a mitochondrial protein, and disruption of a frataxin homolog in yeast results in increased sensitivity to oxidant stress, increased mitochondrial iron and respiration deficiency. These previous data support the hypothesis that FRDA is a disease of mitochondrial oxidative stress, a hypothesis we have tested in cultured cells from FRDA patients. FRDA fibroblasts were hypersensitive to iron stress and significantly more sensitive to hydrogen peroxide than controls. The iron chelator deferoxamine rescued FRDA fibroblasts more than controls from oxidant-induced death, consistent with a role for iron in the differential kinetics of death; however, mean mitochondrial iron content in FRDA fibroblasts was increased by only 40%. Treatment of cells with the intracellular Ca2+chelator BAPTA-AM rescued both FRDA fibroblasts and controls from oxidant-induced death. Treatment with apoptosis inhibitors rescued FRDA but not control fibroblasts from oxidant stress, and staurosporine-induced caspase 3 activity was higher in FRDA fibroblasts, consistent with the possibility that an apoptotic step upstream of caspase 3 is activated in FRDA fibroblasts. These results demonstrate that FRDA fibroblasts are sensitive to oxidant stress, and may be a useful model in which to elucidate the FRDA mechanism and therapeutic strategies.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Apoptosis: DE, drug effects
Base Sequence
Calcium: ME, metabolism
Case-Control Studies
Caspases: ME, metabolism
Cell Line
Chelating Agents: PD, pharmacology
DNA Primers: GE, genetics
Deferoxamine: PD, pharmacology
Egtazic Acid: AA, analogs & derivatives
Egtazic Acid: PD, pharmacology
Fibroblasts: DE, drug effects
Fibroblasts: ME, metabolism
Fibroblasts: PA, pathology
***Friedreich Ataxia: GE, genetics**
***Friedreich Ataxia: ME, metabolism**
**Friedreich Ataxia: PA, pathology**
Hydrogen Peroxide: PD, pharmacology
Iron: ME, metabolism
Iron: PD, pharmacology
*Iron-Binding Proteins
*Mutation
*Oxidative Stress
Phosphotransferases (Alcohol Group Acceptor): GE, genetics
**Pyruvic Acid: PD, pharmacology**
RNA, Messenger: GE, genetics
RNA, Messenger: ME, metabolism
Uridine: PD, pharmacology
CAS REGISTRY NO.: 127-17-3 (Pyruvic Acid); 139890-68-9 (1,2-bis(2-aminophenoxy)ethane N,N,N',N'-tetraacetic acid

acetoxymethyl ester); 58-96-8 (Uridine); 67-42-5 (Egtazic Acid); 70-51-9 (Deferoxamine); 7439-89-6 (Iron); 7440-70-2 (Calcium); 7722-84-1 (Hydrogen Peroxide)
CHEMICAL NAME: 0 (Chelating Agents); 0 (DNA Primers); 0 (Iron-Binding Proteins); 0 (RNA, Messenger); 0 (frataxin); EC 2.7.1 (Phosphotransferases (Alcohol Group Acceptor)); EC 3.4.22.- (Caspases); EC 3.4.22.- (caspase-3)

L124 ANSWER 6 OF 29 MEDLINE on STN
ACCESSION NUMBER: 84139170 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6366288
TITLE: Rationale and indications for the use of alpha-keto analogues.
AUTHOR: Walser M
CONTRACT NUMBER: AM-28527 (NIADDK)
AM-32008 (NIADDK)
AM-32009 (NIADDK)
SOURCE: JPEN. Journal of parenteral and enteral nutrition, (1984 Jan-Feb) 8 (1) 37-41. Ref: 72
Journal code: 7804134. ISSN: 0148-6071.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198404
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 20000303
Entered Medline: 19840425
CONTROLLED TERM: Check Tags: Human; Support, U.S. Gov't, P.H.S.
*Amino Acids: TU, therapeutic use
Amino Acids, Branched-Chain: ME, metabolism
Amino Acids, Branched-Chain: TU, therapeutic use
Amino Acids, Essential: ME, metabolism
Animals
Energy Metabolism
Hepatic Encephalopathy: TH, therapy
Keto Acids: ME, metabolism
***Keto Acids: TU, therapeutic use**
Kidney Failure, Chronic: TH, therapy
**Muscular Dystrophies: GE, genetics**
**Muscular Dystrophies: TH, therapy**
CAS REGISTRY NO.: 1460-34-0 (alpha-keto-beta-methylvaleric acid); **759-05-7 (alpha-ketoisovalerate); 816-66-0 (alpha-ketoisocaproic acid)**
CHEMICAL NAME: 0 (Amino Acids); 0 (Amino Acids, Branched-Chain); 0 (Amino Acids, Essential); 0 (Keto Acids)

L124 ANSWER 7 OF 29 MEDLINE on STN
ACCESSION NUMBER: 82258725 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7104888
TITLE: Quantitative metabolic profiling of alpha-keto acids in Friedreich's ataxia.
AUTHOR: Bertrand M J; Bouchard R; Gauthier G L; Bouchard J P; Barbeau A
SOURCE: Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques, (1982 May) 9 (2) 231-4.
Journal code: 0415227. ISSN: 0317-1671.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 198210
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 20000303
Entered Medline: 19821012

ABSTRACT:
The plasma distribution of alpha-keto acids was measured in 26 subjects including 8 patients with Friedreich's ataxia, 8 with the recessive spastic ataxia of Charlevoix-Sageunay and 10 healthy volunteers. The groups were matched with regards to age, sex, weight and the study was conducted under standardized dietary intake. The result indicate significant differences in the alpha-keto acids distribution between the groups.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't
Adult
***Friedreich Ataxia: BL, blood**
*Keto Acids: BL, blood
Ketoglutaric Acids: BL, blood
Phenylpyruvic Acids: BL, blood
Pyruvates: BL, blood
Pyruvic Acid

CAS REGISTRY NO.: 127-17-3 (Pyruvic Acid); 328-50-7 (alpha-ketoglutaric acid); **816-66-0 (alpha-ketoisocaproic acid)**

CHEMICAL NAME: 0 (Keto Acids); 0 (Ketoglutaric Acids); 0 (Phenylpyruvic Acids); 0 (Pyruvates)

L124 ANSWER 8 OF 29 MEDLINE on STN
ACCESSION NUMBER: 81018958 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6774606
TITLE: Decarboxylation of alpha-ketoisovaleric acid after oral administration in man.
AUTHOR: Epstein C M; Chawla R K; Wadsworth A; Rudman D
CONTRACT NUMBER: AM15736-08 (NIADDK)
RR00039-19 (NCRR)
SOURCE: American journal of clinical nutrition, (1980 Sep) 33 (9) 1968-74.
Journal code: 0376027. ISSN: 0002-9165.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198011
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 20000303
Entered Medline: 19801120

ABSTRACT:
The keto analogues of essential amino acids represent a promising therapeutic modality in hereditary and acquired disorders of nitrogen metabolism. The utilization of these substances in humans has been assayed primarily by nitrogen balance studies. A simple and accurate breath excretion test for 14CO2 enabled us to measure the decarboxylation of 1-14C-alpha-ketoisovaleric acid (KIV, the keto analogue of valine) in two normal and six diseased subjects. Normal volunteers as well as patients with gastrectomy, hepatic failure, renal failure, and myotonic dystrophy were tested in 5-g protein diets supplemented with essential amino acids and KIV (in place of valine). The normal volunteers and the gastrectomy patient were then restudied on 120 g protein/day. With low protein intake, 13 to 32% of ingeted KIV underwent rapid decarboxylation, and this proportion appeared to correlate inversely with damage to organ systems containing the branched-chain keto acid dehydrogenase. With high protein intake, the proportion decarboxylated rose to 44 to 53%. Thse results confirm that the decarboxylation of KIV in man varies under different conditions of dietary intake and metabolic disease. The 14CO2 brewth excretion test is applicable to other related analyses of carboxylic acid

metabolism in human subjects.
CONTROLLED TERM: Check Tags: Human; Support, U.S. Gov't, P.H.S.
Adult
Amino Acids, Essential: AD, administration & dosage
Carbon Dioxide
Decarboxylation
*Dietary Proteins: AD, administration & dosage
Gastrectomy
*Keto Acids: ME, metabolism
Kidney Failure, Chronic: ME, metabolism
Liver Cirrhosis: ME, metabolism
Middle Aged
**Myotonic Dystrophy: ME, metabolism**
Nitrogen: ME, metabolism
Respiration
Structure-Activity Relationship
CAS REGISTRY NO.: 124-38-9 (Carbon Dioxide); **759-05-7 (alpha-ketoisovalerate)**; 7727-37-9 (Nitrogen)
CHEMICAL NAME: 0 (Amino Acids, Essential); 0 (Dietary Proteins); 0 (Keto Acids)

L124 ANSWER 9 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:633291 CAPLUS
DOCUMENT NUMBER: 141:167811
TITLE: Treatment of polyglutamine disorders caused by expanding genomic CAG nucleotides
INVENTOR(S): Brusilow, William S.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 7 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 2004152778 | A1 | 20040805 | US 2004-758415 | | 20040116 |
| PRIORITY APPLN. INFO.: | | | US 2003-440627P | P | 20030117 |

ED Entered STN: 06 Aug 2004
AB The present invention relates to the treatment or prevention of neurodegenerative polyglutamine diseases by the administration of effective amts. of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and/or branched chain .alpha.-keto acids. In particular, the present invention relates to the treatment or prevention of Huntington's disease and other polyglutamine disorders caused by expanded genomic CAG nucleotides.
IT **61-90-5**, Leucine, biological studies **72-18-4**, Valine, biological studies **73-32-5**, Isoleucine, biological studies
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(branched chain .alpha.-keto acids derived from; treatment of polyglutamine disorders caused by expanding genomic CAG nucleotides)
IT **26700-71-0**, Polyglutamine
RL: **ADV (Adverse effect, including toxicity)**; BSU (Biological study, unclassified); BIOL (Biological study)
(treatment of polyglutamine disorders caused by expanding genomic CAG nucleotides)
IT **21752-32-9**, L-Methionine S-sulfoximine **51276-47-2**,

Glufosinate
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(treatment of polyglutamine disorders caused by expanding genomic CAG nucleotides)

L124 ANSWER 10 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:60248 CAPLUS
DOCUMENT NUMBER: 140:105331
TITLE: Use of amino acids for treatment of various conditions
INVENTOR(S): Guttuso, Thomas J., Jr.
PATENT ASSIGNEE(S): University of Rochester, USA
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004006841 | A2 | 20040122 | WO 2003-US21785 | 20030714 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-395975P P 20020712
ED Entered STN: 26 Jan 2004
AB A method of treating a patient for a condition characterized by symptoms that can be alleviated by interfering with or supplementing the activity of endogenous ligands on the a2S subunit of a voltage gated calcium channel, said method comprising: administering to a patient experiencing the condition an amt. of one or more of L-norleucine, L-isoleucine, L-alloisoleucine, L-methionine, L-leucine, 2-cyclohexylglycine, 2-phenylglycine, 2-amino-2-norbornane carboxylic acid, 1-aminocyclohexane carboxylic acid, 2-aminoheptanoic acid, 2-aminocaprylic acid, and 2-aminononanoic acid under conditions effective to treat the condition, wherein when the condition is a hot flash or a symptom of hormonal variation, the compd. is not L-leucine.
IT **61-90-5**, L-Leucine, biological studies **73-32-5**, L-Isoleucine, biological studies
RL: **PAC (Pharmacological activity); THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(use of amino acids for treatment of various conditions such as hot flash and symptoms of hormonal variation in relation to mediation of a2S subunit of voltage gated calcium channels)

L124 ANSWER 11 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:18723 CAPLUS
DOCUMENT NUMBER: 140:71049
TITLE: Novel compositions and methods for treating neurological disorders and associated gastrointestinal conditions
INVENTOR(S): Brudnak, Mark A.
PATENT ASSIGNEE(S): MAK Wood, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 13 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2004005304 | A1 | 20040108 | US 2002-191385 | 20020708 |

PRIORITY APPLN. INFO.: US 2002-191385 20020708
ED Entered STN: 09 Jan 2004
AB The present invention provides therapeutic compns. and methods for treating to neurol. disorders and assocd. gastrointestinal conditions using enhancer mols. These enhancer mols. comprise therapeutically effective amts. of metals, amino acids, polypeptides, saccharides, probiotics, and combinations thereof to enhance expression of genes, and/or enzymic activity of gastrointestinal proteins.
IT **72-18-4**, Valine, biological studies **73-32-5**, Isoleucine, biological studies
RL: BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(compns. of peptides, metals, saccharides, and probiotics for treating neurol. disorders and assocd. gastrointestinal conditions)

L124 ANSWER 12 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:696654 CAPLUS
DOCUMENT NUMBER: 139:229691
TITLE: Nutritional supplement containing creatine, an acid component and/or a complexing agent for improvement of muscle and nerve health.
INVENTOR(S): Purpura, Martin; Jaeger, Ralf; Koenig, Harro
PATENT ASSIGNEE(S): Degussa Bioactives G.m.b.H., Germany
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003071884 | A1 | 20030904 | WO 2003-EP2042 | 20030227 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10208568 | A1 | 20030918 | DE 2002-10208568 | 20020227 |

PRIORITY APPLN. INFO.: DE 2002-10208568 A 20020227
ED Entered STN: 05 Sep 2003
AB The invention relates to a compd. contg. creatine, an acid component and/or a complexing agent. The invention also relates to methods for producing said compd., to a formulation contg. the same, and to the use of the inventive compd.
IT **61-90-5**, L-Leucine, biological studies **72-18-4**,

L-Valine, biological studies **73-32-5**, L-Isoleucine, biological studies
RL: COS (Cosmetic use); FFD (Food or feed use); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(nutritional supplement contg. creatine, an acid component and/or a complexing agent for improvement of muscle and nerve health.)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L124 ANSWER 13 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:454101 CAPLUS
DOCUMENT NUMBER: 139:30834
TITLE: Treatment of CNS disorders using D-amino acid oxidase and D-aspartate oxidase inhibitors
INVENTOR(S): Moser, Paul
PATENT ASSIGNEE(S): Genset S.A., Fr.
SOURCE: PCT Int. Appl., 152 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003047558 | A2 | 20030612 | WO 2002-IB4805 | 20021029 |
| WO 2003047558 | A3 | 20040325 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-336583P P 20011203
ED Entered STN: 13 Jun 2003
AB The present invention relates to compds. that are inhibitors of D-amino acid oxidase, D-aspartate oxidase, or g34872; methods of treating CNS disorders including spinocerebellar ataxia, CAG repeat disorders, and other ataxic disorders using the compds.; and pharmaceutically acceptable compns. that contain the inhibitors are disclosed.
IT **61-90-5P**, L-Leucine, biological studies
RL: PNU (Preparation, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(treatment of CNS disorders using D-amino acid oxidase and D-aspartate oxidase inhibitors)

L124 ANSWER 14 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:833099 CAPLUS
DOCUMENT NUMBER: 135:362605
TITLE: Nutritional preparation comprising ribose and folic acid and medical use thereof
INVENTOR(S): Hageman, Robert Johan Joseph; Smeets, Rudolf Leonardus Lodewijk; Verlaan, George
PATENT ASSIGNEE(S): N.V. Nutricia, Neth.
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001085178 | A1 | 20011115 | WO 2001-NL349 | 20010508 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6420342 | B1 | 20020716 | US 2000-566381 | 20000508 |
| EP 1282426 | A1 | 20030212 | EP 2001-930315 | 20010508 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2003532679 | T2 | 20031105 | JP 2001-581831 | 20010508 |
| US 2002183263 | A1 | 20021205 | US 2002-178736 | 20020625 |
| US 6548483 | B2 | 20030415 | | |

PRIORITY APPLN. INFO.: US 2000-566381 A 20000508
WO 2001-NL349 W 20010508

ED Entered STN: 16 Nov 2001

AB Trauma, surgery, inflammation, subfertility, lactation problems, gut disorders, infant nutrition, cancer, arthritis and other joint problems, vascular problems and cardio- or cerebrovascular problems, ischemia, aging, impaired immune function, burns, sepsis, malnutrition, problems with liver or kidneys, malaria, cystic fibrosis, migraine, neurol. problems, respiratory infections, improvement of sports results, muscle soreness, drug intoxication and pain can be treated with a nutritional compn. contg. effective amts. of ribose and folic acid, optionally combined with other components such as niacin, histidine, glutamine, orotate, vitamin B6 and other components.

IT **61-90-5**, L-Leucine, biological studies **73-32-5**, L-Isoleucine, biological studies
RL: FFD (Food or feed use); MOA (Modifier or additive use); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(nutritional prepn. comprising ribose and folic acid and medical use)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L124 ANSWER 15 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:703775 CAPLUS
DOCUMENT NUMBER: 135:247229
TITLE: Sugars and amino acids for passage through the blood-brain barrier
INVENTOR(S): Naito, Albert T.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 6 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6294520 | B1 | 20010925 | US 1989-341487 | 19890327 |

PRIORITY APPLN. INFO.: US 1989-341487 19890327

ED Entered STN: 26 Sep 2001
AB A material which has the ability to effect it's passage, at least in part, and the ability to transport other materials through the blood-brain barrier which includes any one or more pure sugars or pure amino sugars from the group consisting of meso ethritol, xylitol, D(+)galactose, D(+)lactose, D(+)xylose, dulcitol, myo-inositol, L(-)fructose, D(-)mannitol, sorbitol, D(+)glucose, D(+)arabinose, D(-)arabinose, cellobiose, D(+)maltose, D(+)raffinose, L(+)rhamnose, D(+)melibiose, D(-)ribose, adonitol, D(+)arabitol, L(-)arabitol, D(+)fucose, L(-)fucose, D(-)lyxose, L(+)lyxose, L(-)lyxose, D(+)glucosamine, D-mannosamine, and D-galactosamine; and any one or more amino acids from the group consisting of arginine, asparagine, aspartic acid, cysteine, glutamic acid, glycine, histidine, leucine, methionine, phenylalanine, proline, serine, threonine, glutamine, lysine, tryptophan, tyrosine, valine, and taurine. For use in the research or treatment of a subject that material is combined with one or more of the substances beta carotene, xanthophyll, lecithin, calcium, somatostatin, vasopressin, endorphin, enkephalin, acetyl-L-carnitine, GABA, dynorphin, L-tryptophan, choline, thiamine, pyridoxine, niacin, L-arginine, hydroxyproline, NGF, methionine, cystine, potassium, phosphorus, chlorine, sodium, vitamins A, B, C, D and E, and selenium. Thus, combination of 0.2-6 g of above sugars and 10-3000 mg of above amino acids and 30 mg beta carotene is used for research or treatment of baldness.
IT **61-90-5**, Leucine, biological studies **72-18-4**, Valine, biological studies
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(sugars and amino acids for passage through blood-brain barrier)
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L124 ANSWER 16 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:608584 CAPLUS
DOCUMENT NUMBER: 133:187987
TITLE: Methods using pyrimidine-based nucleosides for treatment of mitochondrial disorders
INVENTOR(S): Naviaux, Robert K.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000050043 | A1 | 20000831 | WO 2000-US4663 | 20000223 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| NZ 513926 | A | 20010928 | NZ 2000-513926 | 20000223 |
| BR 2000008447 | A | 20020115 | BR 2000-8447 | 20000223 |
| EP 1171137 | A1 | 20020116 | EP 2000-910321 | 20000223 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, | | | | |

IE, SI, LT, LV, FI, RO
JP 2002537340 T2 20021105 JP 2000-600654 20000223
PRIORITY APPLN. INFO.: US 1999-121588P P 19990223
WO 2000-US4663 W 20000223
OTHER SOURCE(S): MARPAT 133:187987
ED Entered STN: 01 Sep 2000
AB Methods are provided for the treatment of mitochondrial disorders. The methods include the administration of a pyrimidine-based nucleoside, e.g. triacetyluridine. Also provided are methods of reducing or eliminating symptoms assocd. with mitochondrial disorders. Mitochondrial disorders particularly appropriate for treatment include those attributable to a deficiency of one or more pyrimidines.
IT **61-90-5D**, L-Leucine, pyrimidine nucleoside derivs., biological studies **72-18-4D**, L-Valine, pyrimidine nucleoside derivs., biological studies **73-32-5D**, L-Isoleucine, pyrimidine nucleoside derivs., biological studies
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(pyrimidine-based nucleoside for treatment of mitochondrial disorder)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L124 ANSWER 17 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:655227 CAPLUS
DOCUMENT NUMBER: 123:40968
TITLE: Combination of sugars with amino acids and other drugs
INVENTOR(S): Naito, Albert
PATENT ASSIGNEE(S): USA
SOURCE: Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 652012 | A1 | 19950510 | EP 1993-308852 | 19931105 |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: EP 1993-308852 19931105
ED Entered STN: 05 Jul 1995
AB A material which has the ability to effect it's passage, at least in part, and the ability to transport other materials through the blood-brain barrier, includes any one or more pure sugars or pure amino sugars from the group consisting of meso-erythritol, xylitol, D-galactose, D-lactose, D-xylose, dulcitol, myo-inositol, L-fructose, D-mannitol, sorbitol, D-glucose, D-(+)-arabinose, D-(-)-arabinose, cellobiose, D-(+)-maltose, D-(+)-raffinose, L-(+)-rhamnose, D-(+)-melibiose, D-(-)-ribose, adonitol, D-(+)-arabitol, L-(-)-arabitol, D-(+)-fucose, L-(-)-fucose, D(-)-lyxose, L-(+)-lyxose, L-(-)-lyxose, D-(+)-glucosamine, D-mannosamine, and D-galactosamine; and any one or more amino acids from the group consisting of arginine, asparagine, aspartic acid, cysteine, glutamic acid, glycine, histidine, leucine, methionine, phenylalanine, proline, serine, threonine, glutamine, lysine, tryptophan, tyrosine, valine, and taurine. For use in the research or treatment of a subject that material is combined with one or more of the substances .beta.-carotene, xanthophyll, lecithin, calcium, somatostatin, vasopressin, endorphin, enkephalin, acetyl-L-carnitine, GABA, dynorphin, L--tryptophan, choline, thiamine, pyridoxine, niacin, L-arginine, hydroxyproline, NGF, methionine, cystine, potassium, phosphorus, chlorine, sodium, vitamin A, B, C, D and E, tricalcium phosphate, linolenic acid, oats, rice, apple fiber, acidophilus, and

selenium.
IT **61-90-5**, Leucine, biological studies **72-18-4**, Valine, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(combination of sugars with amino acids and drugs for delivery through blood-brain barrier)

L124 ANSWER 18 OF 29 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:674758 CAPLUS
DOCUMENT NUMBER: 123:102699
TITLE: Efficacy of drug regimen exceeds electrostimulation in treatment of avian **muscular dystrophy**
AUTHOR(S): Hudecki, Michael S.; Povoski, Stephen P.; Gregorio, Carol C.; Granchelli, Joseph A.; Pollina, Catherine M.
CORPORATE SOURCE: Department of Biological Sciences, State University of New York, Buffalo, NY, 14260-1300, USA
SOURCE: Journal of Applied Physiology (1995), 78(6), 2014-19
CODEN: JAPHEV; ISSN: 8750-7587
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 14 Jul 1995
AB Autosomal-recessive dystrophic chickens were treated in three exptl. groups with an i.p. multicomponent drug mixt. (50 mg/kg Ep475, 20 mg/kg Cinanserin, 10 mg/kg stanazolol, 100 mg/kg leucine, 0.1 mg/kg insulin, 100 mg/kg glucose, and 50 mg/kg carnitine), percutaneous high-frequency electrostimulation of the pectoralis muscle, or a combination of both drug and electrostimulation treatments. Therapeutic efficacy was detd. in each group by measurements of strength, righting ability, and histomorphometric analyses of the pectoralis musculature. Drug treatment alone was found to significantly improve muscular strength, function, and relative myofiber necrosis compared with sham-injected controls. The efficacy of drug treatment was equal to or better than singular electrostimulation treatment; there was no apparent additive effect of electrostimulation. As a result, these findings support the use of drug treatment as a useful nongenetic approach to the management of human muscular dystrophy where there is the potential risk of injury from exercise usage.
IT **61-90-5**, Leucine, biological studies
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(multicomponent drug mixt. regimen for management of human **muscular dystrophy** with potential risk of exercise injury)

L124 ANSWER 19 OF 29 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN DUPLICATE 2
ACCESSION NUMBER: 2004-0255018 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Neuroprotective effects of M826, a reversible caspase-3 inhibitor, in the rat malonate model of **Huntington**'s disease
AUTHOR: TOULMOND Sylvie; TANG Keith; BUREAU Yves; ASHDOWN Helen; DEGEN Sarah; O'DONNELL Ruth; TAM John; YONGXIN HAN; COLUCCI John; GIROUX Andre; YANXIA ZHU; BOUCHER Mathieu; PIKOUNIS Bill; XANTHOUDAKIS Steven; ROY Sophie; RIGBY Michael; ZAMBONI Robert; ROBERTSON George S.; NG Gordon Y. K.; NICHOLSON Donald W.;

FLUECKIGER Jean-Pierre
CORPORATE SOURCE: Department of Pharmacology, Merck Frosst Centre for Therapeutic Research, 16711 Trans Canada Highway, Kirkland, Quebec, H9H 3L1, Canada; MSDRL, Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR, United Kingdom; Merck & Co., Inc., 126 E. Lincoln Ave, Rahway, New Jersey 07065, United States
SOURCE: British journal of pharmacology, (2004), 141(4), 689-697, refs. 1 p.1/4
ISSN: 0007-1188 CODEN: BJPCBM
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-4509, 354000117194820170
ABSTRACT: 1 Caspases, key enzymes in the apoptosis pathway, have been detected in the brain of HD patients and in animal models of the disease. In the present study, we investigated the neuroprotective properties of a new, reversible, caspase-3-specific inhibitor, M826 (3-( (2S)-2-[5-tert-butyl-3- [(4-methyl-1,2,5-oxadiazol-3-yl)methyl]amino -2-oxopyrazin-1(2H)-yl]butanoyl amino)-5-[hexyl(methyl) amino]-4-**oxopentanoic** acid), in a rat malonate model of HD. 2 Pharmacokinetic and autoradiography studies after intrastriatal (i.str.) injection of 1.5 nmol of M826 or its tritiated analogue [.sup.3H]M826 indicated that the compound diffused within the entire striatum. The elimination half-life (T.sub.1.sub./.sub.2) of M826 in the rat striatum was 3 h. 3 Lstr. injection of 1.5 nmol of M826 10 min after malonate infusion induced a significant reduction (66%) in the number of neurones expressing active caspase-3 in the ipsilateral striatum. 4 Inhibition of active caspase-3 translated into a significant but moderate reduction (39%) of the lesion volume, and of cell death (24%), 24 h after injury. The efficacy of M826 at inhibiting cell death was comparable to that of the noncompetitive NMDA receptor antagonist MK801. 5 These data provide in vivo proof-of-concept of the neuroprotective effects of reversible caspase-3 inhibitors in a model of malonate-induced striatal injury in the adult rat.
CLASSIFICATION CODE: 002B17G; Life sciences; Medical sciences; Neurology, Nervous system
002B17A01; Life sciences; Medical sciences; Neurology, Nervous system
CONTROLLED TERM: Cysteine endopeptidases; Inhibitor; Animal model; **Huntington** disease; Rat; Animal; Apoptosis; Cell death; Caspase
BROADER TERM: Peptidases; Hydrolases; Enzyme; Rodentia; Mammalia; Vertebrata; Genetic disease; Nervous system diseases; Cerebral disorder; Extrapyramidal syndrome; Degenerative disease; Central nervous system disease

L124 ANSWER 20 OF 29 on STN PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED.
ACCESSION NUMBER: 1990-0104648 PASCAL
TITLE (IN ENGLISH): Glutamine synthetase inhibition by **methionine -sulfoximine** fails to modify kainic acid induced striatal damage
AUTHOR: COHEN M. R.; NANJEGOWDA SRIDHARA; RAMCHAND C. N.
CORPORATE SOURCE: Univ. South Carolina, school medicine, Columbia SC

29202, United States
SOURCE: Research Communications in Psychology, Psychiatry and Behavior, (1988), 13(4), 309-312, 23 refs.
ISSN: 0362-2428 CODEN: RCPBDC
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: CNRS-17440
CLASSIFICATION CODE: 002B03L06; Life sciences; Medical sciences; Toxicology
CONTROLLED TERM: **Huntington** disease; Excitatory aminoacid; Glutamine synthetase; Enzymatic activity; Nervous system diseases; Rat; Animal
BROADER TERM: Rodentia; Mammalia; Vertebrata

L124 ANSWER 21 OF 29 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-441340 [47] WPIDS
CROSS REFERENCE: 2002-017589 [02]
DOC. NO. CPI: C2001-133250
TITLE: New N-glyoxyl-, N-sulfonyl-, 1-carbonyl- and 1-aminocarbonyl- cyclic aza derivatives used for treating e.g. Alzheimer's disease, Parkinson's disease, visual disorders and alopecia.
DERWENT CLASS: B03
INVENTOR(S): HAMILTON, G S; HUANG, W; WU, Y
PATENT ASSIGNEE(S): (GPIN-N) GPI NIL HOLDINGS INC; (HAMI-I) HAMILTON G S; (HUAN-I) HUANG W; (WUYY-I) WU Y
COUNTRY COUNT: 95
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG | MAIN IPC |
|---|---|---|---|---|---|---|
| WO 2001036388 | A1 | 20010525 | (200147)* | EN | 105 | C07D231-04 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW | | | | | | |
| W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW | | | | | | |
| AU 2000069428 | A | 20010530 | (200152) | | | C07D231-04 |
| US 2002028814 | A1 | 20020307 | (200221) | | | C07D413-02 |
| US 6417189 | B1 | 20020709 | (200253) | | | A61K031-495 |
| EP 1242383 | A1 | 20020925 | (200271) | EN | | C07D231-04 |
| R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI | | | | | | |
| JP 2003514799 | W | 20030422 | (200336) | | 82 | C07D231-04 |
| MX 2002004710 | A1 | 20020901 | (200370) | | | C07D231-04 |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| WO 2001036388 | A1 | | WO 2000-US23603 | 20000828 |
| AU 2000069428 | A | | AU 2000-69428 | 20000828 |
| US 2002028814 | A1 | Provisional | US 1999-164950P | 19991112 |
| | | CIP of | US 2000-551618 | 20000417 |
| | | | US 2001-835523 | 20010417 |
| US 6417189 | B1 | Provisional | US 1999-164950P | 19991112 |
| | | | US 2000-551618 | 20000417 |
| EP 1242383 | A1 | | EP 2000-957870 | 20000828 |
| | | | WO 2000-US23603 | 20000828 |
| JP 2003514799 | W | | WO 2000-US23603 | 20000828 |

| | | | |
|---|---|---|---|
| | | JP 2001-538878 | 20000828 |
| MX 2002004710 | A1 | WO 2000-US23603 | 20000828 |
| | | MX 2002-4710 | 20020509 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 2000069428 | A | Based on | WO 2001036388 |
| EP 1242383 | A1 | Based on | WO 2001036388 |
| JP 2003514799 | W | Based on | WO 2001036388 |
| MX 2002004710 | A1 | Based on | WO 2001036388 |

PRIORITY APPLN. INFO: US 2000-551618 20000417; US
1999-164950P 19991112; US
2001-835523 20010417

INT. PATENT CLASSIF.:
MAIN: A61K031-495; C07D231-04; C07D413-02
SECONDARY: A61K031-415; A61K031-4155; A61K031-4245; A61K031-4439; A61K031-50; A61K031-501; A61K031-5025; A61K031-551; A61K031-675; A61K045-00; A61P021-00; A61P025-00; A61P025-16; A61P025-28; C07D231-02; C07D237-04; C07D243-00; C07D401-00; C07D401-06; C07D401-12; C07D403-02; C07D487-04

BASIC ABSTRACT:

WO 200136388 A UPAB: 20031030

NOVELTY - N-glyoxyl cyclic aza derivatives (I) and their salts, esters and solvates, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(A) new N-sulfonyl cyclic aza derivatives (II), their esters and solvates;

(B) new tertiary N-aminocarbonyl cyclic aza derivatives (III), their esters and solvates;

(C) new secondary N-aminocarbonyl cyclic aza derivatives (IV), their esters and solvates.

ACTIVITY - Neuroprotective; nootropic; antiparkinsonian; cerebroprotective; analgesic; ophthalmological.

Four week old male CD1 white mice were dosed intraperitoneally with MPTP (not defined; 30 mg/kg) for 5 days. 4-Phenylbutyl-2-(3,3-dimethyl-2-**oxopentanoyl**)perhydropyridazincarboxylate (IIa) (4 mg/kg) was administered subcutaneously for the same 5 days and for a further 5 days. After 18 days, the level of MPTP lesioning of dopaminergic neurons was evaluated.

Results showed that (IIa) gave a Ki value of 1175 nM and recovery of tyrosine hydroxylase stained dopaminergic neurons of 14 % at 4 mg/kg.

MECHANISM OF ACTION - FKBP-type immunophilin agonist; prolyl-peptidyl cis-trans isomerase inhibitor; prolyl-peptidyl cis-trans romase inhibitor.

USE - Used for effecting neuronal activity, particularly stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration and treatment of neurological disorders, including peripheral neuropathy caused by physical injury or disease, traumatic injury to the brain, physical damage to the spinal cord, stroke associated with brain damage and neurological disorders relating to neurodegeneration, particularly Alzheimer's disease, Parkinson's disease, **Huntington**'s disease, amyotrophic lateral sclerosis, trigeminal neuralgia, glossopharyngeal neuralgia, Bell's palsy, myasthenia gravis, **muscular dystrophy**, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured or prolapsed invertebrate disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndrome, and peripheral neuropathies. (I)-(IV) Can also be used to treat visual disorders and

alopecia.
Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B07-D08; B07-D10; B14-C01; B14-J01; B14-J01A3; B14-J01A4; B14-J05; B14-N03; B14-S01

L124 ANSWER 22 OF 29 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 94043624 EMBASE
DOCUMENT NUMBER: 1994043624
TITLE: Purification and characterization of kynurenine aminotransferase I from human brain.
AUTHOR: Baran H.; Okuno E.; Kido R.; Schwarcz R.
CORPORATE SOURCE: Maryland Psychiatric Research Center, P.O. Box 21247,Baltimore, MD 21228, United States
SOURCE: Journal of Neurochemistry, (1994) 62/2 (730-738).
ISSN: 0022-3042 CODEN: JONRA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
008 Neurology and Neurosurgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Two kynurenine aminotransferases (KATs), arbitrarily termed KAT I and KAT II, are capable of producing the neuroinhibitory brain metabolite kynurenic acid from L-kynurenine in human brain tissue. Here we describe the purification of KAT I to homogeneity and the subsequent characterization of the enzyme using physicochemical, biochemical, and immunological methods. KAT I was purified from human brain .apprx.2,000-fold with a yield of 2%. Assessed by polyacrylamide gel electrophoresis, KAT I migrated toward the anode as a single protein with a mobility of 0.5. The pure enzyme was found to be a dimer consisting of two identical subunits of .apprx.60 kDa. Among several oxo acids tested, KAT I showed highest activity with 2-oxo-isocaproate. Kinetic analyses of the pure enzyme revealed an absolute K(m) of 2.0 mM and 10.0 mM for L-kynurenine and pyruvate, respectively. KAT I activity was substantially inhibited by L-glutamine, L-phenylalanine, and L-tryptophan, using either pyruvate (1 mM) or 2-oxoisocaproate (1 mM) as a cosubstrate. L-Tryptophan inhibited enzyme activity noncompetitively with regard to pyruvate (K(i) = 480 .mu.M) and competitively with regard to L-kynurenine (K(i) = 200 .mu.M). Anti-KAT I antibodies were produced against pure KAT I and were partially purified by conventional techniques. Immunotitration and immunoblotting analyses confirmed that KAT I is clearly distinct from both human KAT II and rat kynurenine-pyruvate aminotransferase. Pure human KAT I and its antibody will serve as valuable tools in future studies of kynurenic acid production in the human brain under physiological and pathological conditions.

CONTROLLED TERM: Medical Descriptors:
*enzyme purification
adult
article
case report
controlled study
cryoprotection
enzyme activity
enzyme chemistry
enzyme mechanism
human
human tissue
**huntington chorea: ET, etiology**

male
nerve cell degeneration
neurotoxicity
priority journal
Drug Descriptors:
*kynurenine aminotransferase: EC, endogenous compound
2 oxoisocaproic acid
enzyme antibody
isoenzyme: EC, endogenous compound
kynurenic acid
kynurenine
pyruvic acid
tryptophan
CAS REGISTRY NO.: (kynurenine aminotransferase) 9030-38-0; (2 oxoisocaproic acid) **816-66-0**; (kynurenic acid) 492-27-3; (kynurenine) 16055-80-4, 343-65-7; (pyruvic acid) 127-17-3, 19071-34-2, 57-60-3; (tryptophan) 6912-86-3, 73-22-3

L124 ANSWER 23 OF 29 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 82238604 EMBASE
DOCUMENT NUMBER: 1982238604
TITLE: Parenteral branched-chain amino acid treatment and avian dystrophy.
AUTHOR: Hudecki M.S.; Pollina C.M.; Heffner R.R.
CORPORATE SOURCE: Div. Cell Mol. Biol., State Univ. New York, Buffalo, NY 14260, United States
SOURCE: Muscle and Nerve, (1982) 5/6 (447-457).
CODEN: MUNEDE
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
029 Clinical Biochemistry
008 Neurology and Neurosurgery
LANGUAGE: English
ABSTRACT:
Genetically homozygous line 413 dystrophic chickens were given twice-daily intraperitoneal injections of solutions containing branched-chain amino acids (BCAA-leucine, valine, isoleucine) either alone or in combination; and their .alpha.-ketoacid analogs (.alpha.-ketoisocaproic and .alpha.-ketoisovaleric acids). Another trial consisted of an amino acid mixture containing BCAA. Amino acid supplementation in each case significantly prolonged righting ability measured regularly by a standardized flip-test procedure. Enhanced functional ability was not generally accompanied by a decrease in plasma creatine kinase activity. However, a measurable increase in the affected pectoralis major muscle mass and protein content (female chickens in particular) was found with BCAA therapy. Moreover, the increase in muscle bulk was attended in some cases by a reduction in the relative number of degenerating fibers quantitated microscopically. Contrariwise, the amino acid mixture caused a reduction in pectoralis muscle mass. It is concluded that parenteral BCAA therapy offers limited benefit in retarding dystrophic symptoms in the chicken.

CONTROLLED TERM: Medical Descriptors:
*body weight
*dystrophy
*genetic disorder
***muscular dystrophy**
*parenteral nutrition
*pectoralis major muscle
chicken
drug mixture
histology

therapy
muscle
animal experiment
heredity
controlled study
intraperitoneal drug administration
Drug Descriptors:
*2 oxoisocaproic acid
*2 oxoisovaleric acid
*amino acid
*branched chain amino acid
*cinanserin
*creatine kinase
*isoleucine
*leucine
*muscle protein
*valine

CAS REGISTRY NO.: (2 oxoisocaproic acid) **816-66-0**; (2 oxoisovaleric acid) **759-05-7**; (amino acid) 65072-01-7; (cinanserin) 1166-34-3, 54-84-2; (creatine kinase) 9001-15-4; (isoleucine) 7004-09-3, 73-32-5; (leucine) 61-90-5, 7005-03-0; (valine) 7004-03-7, 72-18-4

COMPANY NAME: Sigma (United States); Squibb (United States)

L124 ANSWER 24 OF 29 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1988:156799 BIOSIS
DOCUMENT NUMBER: PREV198885080452; BA85:80452
TITLE: EFFECT OF **KETOLEUCINE** TREATMENT ON ATROPHY OF SKELETAL MUSCLE.
AUTHOR(S): YEE W-C [Reprint author]; DRACHMAN D B; WALSER M; PESTRONK A
CORPORATE SOURCE: DEP NEUROL, JOHNS HOPKINS UNIV SCH MED, BALTIMORE, MD 21205, USA
SOURCE: Experimental Neurology, (1988) Vol. 99, No. 1, pp. 1-9. CODEN: EXNEAC. ISSN: 0014-4886.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 22 Mar 1988
Last Updated on STN: 22 Mar 1988

ABSTRACT:There is a net loss of skeletal muscle protein in muscle-wasting disorders including the **muscular dystrophies** and denervation atrophy. Regardless of the nature of the underlying defect, a treatment that could reduce the rate of muscle protein degradation may be of the therapeutic value in these conditions. **Ketoleucine** (.alpha.-***ketoisocaproic*** acid) has been reported to reduce the rate of protein degradation in skeletal muscle. To evaluate **ketoleucine**'s therapeutic potential, we studied its effect on the muscle protein loss that follows denervation in rats. Maximum tolerated doses of **ketoleucine** were administered twice daily to rats after surgery denervation of one leg. Wet weights and noncollagen proteins of the soleus and extensor digitorum longus muscles were measured. The **ketoleucine**-treated animals failed to show significant decrease in muscle wasting, compared with nontreated denervated controls. Further, urinary 3-methylhistidine excretion, a putative measure of muscle breakdown, was not reduced in **ketoleucine**-treated animals. Our findings do not support the suggested therapeutic role for ***ketoleucine*** in muscle-wasting disease.

CONCEPT CODE: Anatomy and Histology - Experimental anatomy 11104
Chordate body regions - Extremities 11318
Pathology - Necrosis 12510
Urinary system - Physiology and biochemistry 15504

Muscle - Pathology 17506
Nervous system - General and methods 20501
Pharmacology - Muscle system 22022
INDEX TERMS: Major Concepts
Morphology; Muscular System (Movement and Support); Nervous System (Neural Coordination); Pharmacology
INDEX TERMS: Miscellaneous Descriptors
RAT **MUSCULAR DYSTROPHY** DENERVATION SOLEUS EXTENSOR DIGITORUM LONGUS URINARY 3 METHYLHISTIDINE
ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
REGISTRY NUMBER: **816-66-0 (KETOLEUCINE)**
368-16-1 (3-METHYLHISTIDINE)

L124 ANSWER 25 OF 29 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1981:124830 BIOSIS
DOCUMENT NUMBER: PREV198121059826; BR21:59826
TITLE: ACUTE EFFECTS OF BRANCHED CHAIN KETO ACIDS ADMINISTERED AS ORNITHINE SALTS ON MUSCLE PROTEIN DEGRADATION IN DUCHENNES **MUSCULAR DYSTROPHY**.
AUTHOR(S): STEWART P M [Reprint author]; WALSER M; DRACHMAN D B
CORPORATE SOURCE: DEP PHARMACOL, JOHNS HOPKINS SCH MED, BALTIMORE, MD, USA
SOURCE: Clinical Research, (1981) Vol. 29, No. 2, pp. 580A.
Meeting Info.: 94TH ANNUAL MEETING OF THE ASSOCIATION OF AMERICAN PHYSICIANS, SAN FRANCISCO, CALIF., USA, APRIL 25-27, 1981. CLIN RES.
CODEN: CLREAS. ISSN: 0009-9279.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Genetics - Human 03508
Clinical biochemistry - General methods and applications 10006
Biochemistry studies - Proteins, peptides and amino acids 10064
Metabolism - Proteins, peptides and amino acids 13012
Urinary system - Physiology and biochemistry 15504
Muscle - Pathology 17506
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Muscle system 22022
INDEX TERMS: Major Concepts
Genetics; Metabolism; Muscular System (Movement and Support); Pharmacology
INDEX TERMS: Miscellaneous Descriptors
ABSTRACT HUMAN ALPHA KETO ISO CAPROATE METABOLIC-DRUG 3 METHYL HISTIDINE CREATININE PHOSPHO KINASE
ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates,

Vertebrates
REGISTRY NUMBER: 70-26-8QD (ORNITHINE)
616-07-9QD (ORNITHINE)
368-16-1 (3-METHYLHISTIDINE)
**816-66-0** (ALPHA KETO ISO CAPROATE)
7006-33-9DQ (ORNITHINE)

L124 ANSWER 26 OF 29 USPATFULL on STN
ACCESSION NUMBER: 2004:190830 USPATFULL
TITLE: Cellular phosphorylation potential enhancing compositions preparation and use thereof
INVENTOR(S): Bunger, Rolf, McLean, VA, UNITED STATES
Verma, Ajay, North Potomac, MD, UNITED STATES

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2004147604 | A1 | 20040729 |
| APPLICATION INFO.: | US 2003-643080 | A1 | 20030819 (10) |

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-828589, filed on 9 Apr 2001, ABANDONED Continuation-in-part of Ser. No. US 2000-550047, filed on 14 Apr 2000, ABANDONED Continuation-in-part of Ser. No. US 1997-999767, filed on 27 Oct 1997, ABANDONED Continuation of Ser. No. US 1996-643284, filed on 8 May 1996, ABANDONED Continuation-in-part of Ser. No. US 1996-646572, filed on 8 May 1996, GRANTED, Pat. No. US 5714515 Division of Ser. No. US 1994-239635, filed on 9 May 1994, GRANTED, Pat. No. US 5536751
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Werten F.W. Bellamy, Director, Office of Intl Prop Uniformed Services Univ. Of, The Health Sciences, 4301 Jones Bridge Road, Room D3001, Bethesda, MD, 20814-4799
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Page(s)
LINE COUNT: 2180
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A pharmaceutical composition comprising as an active phosphorylation potential enhancing substance a pharmaceutically-acceptable salt of an alpha-keto carboxylic acid thereof alone or in combination with nicatinamide and creatine and, its use and products containing the same.

L124 ANSWER 27 OF 29 USPATFULL on STN
ACCESSION NUMBER: 2004:51576 USPATFULL
TITLE: Compositions useful as inhibitors of GSK-3
INVENTOR(S): Forster, Cornelia J., Pelham, NH, UNITED STATES
Park, Larry C., Waltham, MA, UNITED STATES
Wannamaker, Marion W., Stow, MA, UNITED STATES
Yao, Yung-Mae M., Newton, MA, UNITED STATES

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2004039007 | A1 | 20040226 |
| APPLICATION INFO.: | US 2003-632340 | A1 | 20030801 (10) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2002-400967P | 20020802 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: VERTEX PHARMACEUTICALS INC., 130 WAVERLY STREET, CAMBRIDGE, MA, 02139-4242
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 2000
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a compound of formula I: ##STR1##

or a pharmaceutically acceptable derivative thereof. These compounds are inhibitors of protein kinases, particularly inhibitors of GSK3 mammalian protein kinase. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of utilizing those compounds and compositions in the treatment of various protein kinase mediated disorders.

L124 ANSWER 28 OF 29 USPATFULL on STN
ACCESSION NUMBER: 2002:288136 USPATFULL
TITLE: 1,4-dihydropyridine compounds as bradykinin antagonists
INVENTOR(S): Kawamura, Mitsuhiro, UNITED STATES
Kawai, Makoto, UNITED STATES
Shishido, Yuji, UNITED STATES
Kato, Tomoki, UNITED STATES
Katsu, Yasuhiro, UNITED STATES
Ikeda, Takafumi, UNITED STATES
Murase, Noriaki, UNITED STATES

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2002161006 | A1 | 20021031 | |
| | US 6653313 | B2 | 20031125 | |
| APPLICATION INFO.: | US 2001-903157 | A1 | 20010711 | (9) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2000-224558P | 20000810 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PFIZER INC, 150 EAST 42ND STREET, 5TH FLOOR - STOP 49, NEW YORK, NY, 10017-5612
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
LINE COUNT: 4634
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to compounds of the formula ##STR1##

wherein each A is independently halo; Y is --(CH.sub.2).sub.m--, --C(O)-- or --S(O)--; R.sup.1 and R.sup.2 are independently C.sub.1-4 alkyl; R.sup.3 is substituted azacycloalkyl etc.; R.sup.4 is phenyl substituted at the 2-position with a substituent selected from substituted C.sub.1-7 alkyl, substituted C.sub.1-7 alkoxy, amine, etc; R.sup.5 is hydrogen or C.sub.1-4 alkyl; m is 0, 1 or 2; and n is 0, 1, 2, 3, 4 or 5. The present invention also relates to pharmaceutical compositions containing such compounds and to the use of such compounds in the treatment and prevention of inflammation, asthma, allergic rhinitis, pain and other disorders.

L124 ANSWER 29 OF 29 USPATFULL on STN
ACCESSION NUMBER: 2002:243642 USPATFULL
TITLE: Caspase inhibitors and uses thereof

INVENTOR(S): Golec, Julian M.C., Swindon, UNITED KINGDOM
Charifson, Paul, UNITED STATES
Brenchley, Guy, Oxon, UNITED KINGDOM

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2002132833 | A1 | 20020919 |
| | US 6632962 | B2 | 20031014 |
| APPLICATION INFO.: | US 2001-834052 | A1 | 20010403 (9) |

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2000-US21503, filed on 4 Aug 2000, UNKNOWN

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1999-147706P | 19990806 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Ian Robert Silverman, Vertex Pharmaceuticals Inc., 130 Waverly Street, Cambridge, MA, 02139-4242
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
LINE COUNT: 1234
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides novel compounds that are effective as inhibitors of caspase and cellular apoptosis. The invention also provides methods for using the compounds to treat caspase-mediated diseases in mammals. The compounds have the general formula I: ##STR1##

wherein X is F or Cl; R.sup.1 is COOH, COO(alkyl), or an isostere thereof; and R.sup.2 is an aryl group.

# National Library of Medicine - Medical Subject Headings

**2004 MeSH**

## MeSH Descriptor Data

Return to Entry Page

| | |
|---|---|
| **MeSH Heading** | Riluzole |
| **Tree Number** | D03.383.871.651 |
| **Scope Note** | A glutamate antagonist (RECEPTORS, GLUTAMATE) used as an anticonvulsant (ANTICONVULSANTS) and to prolong the survival of patients with AMYOTROPHIC LATERAL SCLEROSIS. |
| **Entry Term** | 2-Amino-6-trifluoromethoxybenzothiazole |
| **Entry Term** | PK-26124 |
| **Entry Term** | RP-54274 |
| **Entry Term** | Rilutek |
| **Allowable Qualifiers** | AA AD AE AG AI AN BL CF CH CL CS CT DU EC HI IM IP ME PD PK PO RE SD ST TO TU UR |
| **Pharm. Action** | Anesthetics |
| **Pharm. Action** | Anticonvulsants |
| **Pharm. Action** | Excitatory Amino Acid Antagonists |
| **Pharm. Action** | Neuroprotective Agents |
| **Registry Number** | 1744-22-5 |
| **Previous Indexing** | Thiazoles (1986-1997) |
| **History Note** | 98; use RILUZOLE (NM) 1986-97 |
| **Unique ID** | D019782 |

## MeSH Tree Structures

Heterocyclic Compounds [D03]
  Heterocyclic Compounds, 1-Ring [D03.383]
    Thiazoles [D03.383.871]

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=> fil medl
FILE 'MEDLINE' ENTERED AT 15:31:14 ON 28 SEP 2004

 FILE LAST UPDATED: 25 SEP 2004 (20040925/UP). FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d que l89
L8             1 SEA FILE=REGISTRY ABB=ON  CONGO RED/CN
L9             1 SEA FILE=REGISTRY ABB=ON  CYSTAMINE/CN
L10            1 SEA FILE=REGISTRY ABB=ON  CYSTEAMINE/CN
L11            4 SEA FILE=REGISTRY ABB=ON  (MINOCYCLINE/CN OR "MINOCYCLINE
                   BISHYDROCHLORIDE"/CN OR "MINOCYCLINE CHLORIDE"/CN OR "MINOCYCLI
                   NE HYDROCHLORIDE"/CN OR "MINOCYCLINE NITRATE"/CN)
L12            1 SEA FILE=REGISTRY ABB=ON  84494-70-2
L13            1 SEA FILE=REGISTRY ABB=ON  RILUZOLE/CN
L70         5474 SEA FILE=MEDLINE ABB=ON  HUNTINGTON DISEASE/CT
L71         3608 SEA FILE=MEDLINE ABB=ON  SPINOCEREBELLAR DEGENERATIONS+NT/CT
L72        14324 SEA FILE=MEDLINE ABB=ON  MUSCULAR DISORDERS, ATROPHIC+NT/CT
L87         6073 SEA FILE=MEDLINE ABB=ON  (L8 OR L9 OR L10 OR L11 OR L12 OR
                   L13)
L88           25 SEA FILE=MEDLINE ABB=ON  ETHYL EICOSAPENTAENO?
L89           40 SEA FILE=MEDLINE ABB=ON  (L70 OR L71 OR L72) AND (L87 OR L88)


=> d iall l89 1-40; fil hom

L89  ANSWER 1 OF 40     MEDLINE on STN
ACCESSION NUMBER:   2004316278     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 15217383
TITLE:              Deleterious effects of minocycline in animal models of
                    Parkinson's disease and Huntington's disease.
AUTHOR:             Diguet Elsa; Fernagut Pierre-Olivier; Wei Xing; Du
                    Yansheng; Rouland Richard; Gross Christian; Bezard Erwan;
                    Tison Francois
CORPORATE SOURCE:   Physiologie et Physiopathologie de la Signalization
                    Cellulaire, UMR-CNRS 5543, Universite Victor Segalen
                    Bordeaux2, 146 rue Leo Saignat, 33076, Bordeaux, France.
SOURCE:             European journal of neuroscience, (2004 Jun) 19 (12)
                    3266-76.
                    Journal code: 8918110. ISSN: 0953-816X.
PUB. COUNTRY:       France
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200408
ENTRY DATE:         Entered STN: 20040626
                    Last Updated on STN: 20040819
                    Entered Medline: 20040818
ABSTRACT:
```

Minocycline has been shown to exert anti-inflammatory effects underlying its putative neuroprotective properties in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease and in the R6/2 mouse model of Huntington's disease (HD). However, contradictory results have recently been reported. We report deleterious effects of minocycline in two phenotypic (toxic) models of Parkinson's disease and HD in monkey and mouse. Of seven MPTP-intoxicated female cynomolgus monkeys (0.2 mg/kg, i.v. until day 15), three received minocycline (200 mg b.i.d.). While placebo-MPTP-treated animals displayed mild parkinsonism at day 15, the minocycline/MPTP-treated animals tended to be more affected (P = 0.057) and showed a greater loss of putaminal dopaminergic nerve endings (P < 0.0001). In the 3-nitropropionic acid (3-NP) mouse model of HD, minocycline (45 mg/kg i.p.) was administered 30 min before each i.p. injection of 3-NP (b.i.d., cumulated dose, 360 mg/kg in 5 days). Mice receiving minocycline exhibited a worsening of the mean motor score with a slower recovery slope, more impaired general activity and significantly deteriorated performances on the rotarod, pole test and beam-traversing tasks. The histopathological outcome demonstrated that minocycline-treated mice presented significantly more severe neuronal cell loss in the dorsal striatum. The effect of minocycline vs. 3-NP was also investigated on hippocampal and cortical cell cultures. minocycline blocked 3-NP-induced neurotoxicity at certain doses (1 mm cortical neurons) but not at higher doses (10 mm). Thus, minocycline may have variable and even deleterious effects in different species and models according to the mode of administration and dose.

CONTROLLED TERM: Check Tags: Comparative Study; Female; Male; Support, Non-U.S. Gov't
Animals
Cells, Cultured
Convulsants: TO, toxicity
Corpus Striatum: DE, drug effects
*Corpus Striatum: PA, pathology
Disease Models, Animal
**Huntington Disease: CI, chemically induced**
***Huntington Disease: DT, drug therapy**
Immunohistochemistry
Macaca fascicularis
Mice
*Minocycline: AE, adverse effects
Nerve Degeneration: PA, pathology
Neurons: DE, drug effects
Neurons: PA, pathology
*Neuroprotective Agents: AE, adverse effects
*Parkinsonian Disorders: DT, drug therapy
Propionic Acids: TO, toxicity

CAS REGISTRY NO.: **10118-90-8 (Minocycline)**; 504-88-1 (3-nitropropionic acid)

CHEMICAL NAME: 0 (Convulsants); 0 (Neuroprotective Agents); 0 (Propionic Acids)

L89 ANSWER 2 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2004232265 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15131283
TITLE: Huntington's disease. Unorthodox clinical trials meld science and care.
AUTHOR: Couzin Jennifer
SOURCE: Science, (2004 May 7) 304 (5672) 816-7.
Journal code: 0404511. ISSN: 1095-9203.
PUB. COUNTRY: United States
DOCUMENT TYPE: News Announcement
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405

ENTRY DATE: Entered STN: 20040510
Last Updated on STN: 20040528
Entered Medline: 20040527
CONTROLLED TERM: Check Tags: Human
Animals
Blueberry Plant
*Clinical Trials
Creatine: AD, administration & dosage
Creatine: TU, therapeutic use
Cysteamine: AD, administration & dosage
Cysteamine: TU, therapeutic use
Drug Therapy, Combination
Drug Therapy, Computer-Assisted
Fatty Acids, Omega-3: AD, administration & dosage
Fatty Acids, Omega-3: TU, therapeutic use
***Huntington Disease: DT, drug therapy**
Mice
Patient Selection
Phytotherapy
Plant Extracts: AD, administration & dosage
Plant Extracts: TU, therapeutic use
Software
Trehalose: AD, administration & dosage
Trehalose: TU, therapeutic use
Ubiquinone: AD, administration & dosage
Ubiquinone: TU, therapeutic use
CAS REGISTRY NO.: 1339-63-5 (Ubiquinone); 57-00-1 (Creatine); **60-23-1 (Cysteamine)**; 99-20-7 (Trehalose)
CHEMICAL NAME: 0 (Fatty Acids, Omega-3); 0 (Plant Extracts)

L89 ANSWER 3 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2004069301 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14870963
TITLE: Why minocycline is helpful in Huntington's disease.
AUTHOR: Bonelli Raphael M; Kapfhammer Hans-Peter
SOURCE: Journal of psychopharmacology (Oxford, England), (2003 Dec) 17 (4) 461.
Journal code: 8907828. ISSN: 0269-8811.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20040212
Last Updated on STN: 20040510
Entered Medline: 20040507
CONTROLLED TERM: Check Tags: Human
Animals
Anti-Bacterial Agents: PD, pharmacology
*Anti-Bacterial Agents: TU, therapeutic use
Clinical Trials
Cognition: DE, drug effects
***Huntington Disease: DT, drug therapy**
**Huntington Disease: GE, genetics**
Minocycline: PD, pharmacology
*Minocycline: TU, therapeutic use
Motor Activity: DE, drug effects
Motor Activity: GE, genetics
CAS REGISTRY NO.: **10118-90-8 (Minocycline)**
CHEMICAL NAME: 0 (Anti-Bacterial Agents)

L89 ANSWER 4 OF 40 MEDLINE on STN

ACCESSION NUMBER: 2004033165 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14729833
TITLE: Congo red, doxycycline, and HSP70 overexpression reduce aggregate formation and cell death in cell models of oculopharyngeal muscular dystrophy.
AUTHOR: Bao Y P; Sarkar S; Uyama E; Rubinsztein D C
SOURCE: Journal of medical genetics, (2004 Jan) 41 (1) 47-51. Journal code: 2985087R. ISSN: 1468-6244.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20040122
Last Updated on STN: 20040225
Entered Medline: 20040224
CONTROLLED TERM: Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
Animals
COS Cells: CH, chemistry
COS Cells: ME, metabolism
Cell Death: DE, drug effects
Cell Death: GE, genetics
Cell Line
Cercopithecus aethiops
*Congo Red: CH, chemistry
*Doxycycline: PD, pharmacology
*Heat-Shock Proteins 70: BI, biosynthesis
Heat-Shock Proteins 70: IM, immunology
Immunohistochemistry
Inclusion Bodies: DE, drug effects
Inclusion Bodies: ME, metabolism
Middle Aged
***Muscular Dystrophy, Oculopharyngeal: GE, genetics**
**Muscular Dystrophy, Oculopharyngeal: ME, metabolism**
Pharyngeal Muscles: CH, chemistry
Pharyngeal Muscles: ME, metabolism
Poly(A)-Binding Protein II: AN, analysis
Poly(A)-Binding Protein II: GE, genetics
Poly(A)-Binding Protein II: IM, immunology
CAS REGISTRY NO.: 564-25-0 (Doxycycline); **573-58-0 (Congo Red)**
CHEMICAL NAME: 0 (Heat-Shock Proteins 70); 0 (Poly(A)-Binding Protein II)

L89 ANSWER 5 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2004024065 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14663041
TITLE: Dosage effects of riluzole in Huntington's disease: a multicenter placebo-controlled study.
AUTHOR: Anonymous
CORPORATE SOURCE: Huntington Study Group.
CONTRACT NUMBER: FD-R-001671 (FDA)
SOURCE: Neurology, (2003 Dec 9) 61 (11) 1551-6. Journal code: 0401060. ISSN: 1526-632X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200401

ENTRY DATE: Entered STN: 20040116
Last Updated on STN: 20040129
Entered Medline: 20040128

ABSTRACT:
BACKGROUND: Riluzole retards striatal glutamate release and pathologic consequences in neurotoxic animal models of Huntington's disease (HD).
OBJECTIVE: To determine the dosage-related impact of riluzole on chorea in HD.
METHODS: An 8-week double-blind dose-ranging multicenter study of riluzole was conducted in 63 subjects (32 women, 31 men) with HD who were randomized to receive placebo, riluzole 100 mg/day, or riluzole 200 mg/day. The prespecified outcome measure was change in the total maximal chorea score of the Unified Huntington's Disease Rating Scale (UHDRS). RESULTS: Fifty-six (89%) subjects completed the study. A reduction ($p < 0.01$) in chorea at 8 weeks was found using a linear trend test with dose. Comparing the groups individually, the reduction in chorea for the riluzole 200-mg/day group (-2.2 +/- 3.3) was different ($p = 0.01$) from placebo (+0.7 +/- 3.4), but the riluzole 100-mg/day group (-0.2 +/- 2.9) was not. Riluzole did not improve other motor, cognitive, behavioral, or functional components of the UHDRS. Alanine aminotransferase was elevated in a dosage-dependent fashion ($p = 0.01$). CONCLUSIONS: Over 8 weeks of treatment, riluzole 200 mg/day ameliorated chorea intensity in HD without improving functional capacity or other clinical features of illness. Riluzole 200 mg/day was attended by reversible liver transaminase abnormalities that would require monitoring in long-term studies.

CONTROLLED TERM: Check Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Chorea: DT, drug therapy
Dose-Response Relationship, Drug
Double-Blind Method
*Excitatory Amino Acid Antagonists: AD, administration & dosage
Excitatory Amino Acid Antagonists: AE, adverse effects
Excitatory Amino Acid Antagonists: TU, therapeutic use
**Huntington Disease: DI, diagnosis**
***Huntington Disease: DT, drug therapy**
Middle Aged
*Riluzole: AD, administration & dosage
Riluzole: AE, adverse effects
Riluzole: TU, therapeutic use
Treatment Outcome

CAS REGISTRY NO.: **1744-22-5 (Riluzole)**
CHEMICAL NAME: 0 (Excitatory Amino Acid Antagonists)

L89 ANSWER 6 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003603773 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14681898
TITLE: Minocycline is not beneficial in a phenotypic mouse model of Huntington's disease.
COMMENT: Comment on: Ann Neurol. 2003 Aug;54(2):186-96. PubMed ID: 12891671
AUTHOR: Diguet Elsa; Rouland Richard; Tison Francois
SOURCE: Annals of neurology, (2003 Dec) 54 (6) 841-2.
Journal code: 7707449. ISSN: 0364-5134.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031223
Last Updated on STN: 20040115
Entered Medline: 20040114
CONTROLLED TERM: Animals

*Disease Models, Animal
***Huntington Disease: DT, drug therapy**
**Huntington Disease: GE, genetics**
Mice
*Minocycline: TU, therapeutic use
*Neuroprotective Agents: TU, therapeutic use
*Phenotype
CAS REGISTRY NO.: **10118-90-8 (Minocycline)**
CHEMICAL NAME: 0 (Neuroprotective Agents)

L89 ANSWER 7 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003603772 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14681897
TITLE: Minocycline is protective in a mouse model of Huntington's disease.
COMMENT: Comment on: Ann Neurol. 2003 Aug;54(2):186-96. PubMed ID: 12891671
AUTHOR: Hersch Steven; Fink Klaus; Vonsattel Jean Paul; Friedlander Robert M
SOURCE: Annals of neurology, (2003 Dec) 54 (6) 841; author reply 842-3.
Journal code: 7707449. ISSN: 0364-5134.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031223
Last Updated on STN: 20040115
Entered Medline: 20040114
CONTROLLED TERM: Animals
*Disease Models, Animal
***Huntington Disease: DT, drug therapy**
Mice
*Minocycline: TU, therapeutic use
*Neuroprotective Agents: TU, therapeutic use
CAS REGISTRY NO.: **10118-90-8 (Minocycline)**
CHEMICAL NAME: 0 (Neuroprotective Agents)

L89 ANSWER 8 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003421365 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12925002
TITLE: Differential responsiveness of rat striatal nerve endings to the mitochondrial toxin 3-nitropropionic acid: implications for Huntington's disease.
AUTHOR: Marti Matteo; Mela Flora; Ulazzi Linda; Hanau Stefania; Stocchi Sara; Paganini Francesca; Beani Lorenzo; Bianchi Clementina; Morari Michele
CORPORATE SOURCE: Department of Experimental and Clinical Medicine, Section of Pharmacology, via Fossato di Mortara 17-19, 44100 Ferrara, Italy.
SOURCE: European journal of neuroscience, (2003 Aug) 18 (4) 759-67.
Journal code: 8918110. ISSN: 0953-816X.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030910
Last Updated on STN: 20031015
Entered Medline: 20031014

ABSTRACT:
Rat striatal synaptosomes and slices were used to investigate the responsiveness of different populations of nerve terminals to 3-nitropropionic acid (3-NP), a suicide inhibitor of the mitochondrial enzyme succinate dehydrogenase, and to elucidate the ionic mechanisms involved. 3-NP (0.3-3 mm) stimulated spontaneous gamma-aminobutyric acid (GABA), glutamate and [3H]-dopamine efflux but left unchanged acetylcholine efflux from synaptosomes. This effect was associated with a >70% inhibition of succinate dehydrogenase, as measured in the whole synaptosomal population. The facilitation was not dependent on extracellular Ca2+ but relied on voltage-dependent Na+ channel opening, because it was prevented by tetrodotoxin and riluzole. 3-NP also elevated spontaneous glutamate efflux from slices but in a tetrodotoxin-insensitive way. To investigate whether energy depletion could change the responsiveness of nerve endings to a depolarizing stimulus, synaptosomes were pretreated with 3-NP and challenged with pulses of KCl evoking 'quasi-physiological' neurotransmitter release. 3-NP potentiated the K+-evoked GABA, glutamate and [3H]-dopamine release but inhibited the K+-evoked acetylcholine release. The 3-NP induced potentiation of GABA release was Ca2+-dependent and prevented by tetrodotoxin and riluzole whereas the 3-NP-induced inhibition of acetylcholine release was tetrodotoxin- and riluzole-insensitive but reversed by glipizide, an ATP-dependent K+ channel inhibitor. We conclude that the responsiveness of striatal nerve endings to 3-NP relies on activation of different ionic conductances, and suggest that the selective survival of striatal cholinergic interneurons following chronic 3-NP treatment (as in models of Huntington's disease) may rely on the opening of ATP-dependent K+ channels, which counteracts the fall in membrane potential as a result of mitochondrial impairment.

CONTROLLED TERM: Check Tags: Male; Support, Non-U.S. Gov't
Acetylcholine: ME, metabolism
Animals
*Convulsants: PD, pharmacology
*Corpus Striatum: DE, drug effects
Corpus Striatum: ME, metabolism
Dopamine: ME, metabolism
Excitatory Amino Acid Antagonists: PD, pharmacology
Glutamic Acid: DE, drug effects
Glutamic Acid: ME, metabolism
**Huntington Disease: PP, physiopathology**
Mitochondria: ME, metabolism
Organ Culture
Potassium Channels: ME, metabolism
*Propionic Acids: PD, pharmacology
Rats
Rats, Sprague-Dawley
Riluzole: PD, pharmacology
Sodium Channels: ME, metabolism
Succinate Dehydrogenase: ME, metabolism
*Synaptosomes: DE, drug effects
Synaptosomes: ME, metabolism
Tetrodotoxin: PD, pharmacology
gamma-Aminobutyric Acid: DE, drug effects
gamma-Aminobutyric Acid: ME, metabolism

CAS REGISTRY NO.: **1744-22-5 (Riluzole)**; 4368-28-9 (Tetrodotoxin); 504-88-1 (3-nitropropionic acid); 51-61-6 (Dopamine); 51-84-3 (Acetylcholine); 56-12-2 (gamma-Aminobutyric Acid); 56-86-0 (Glutamic Acid)

CHEMICAL NAME: 0 (Convulsants); 0 (Excitatory Amino Acid Antagonists); 0 (Potassium Channels); 0 (Propionic Acids); 0 (Sodium Channels); EC 1.3.99.1 (Succinate Dehydrogenase)

L89 ANSWER 9 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003413850 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12930891
TITLE: Minocycline inhibits caspase-independent and -dependent mitochondrial cell death pathways in models of Huntington's disease.
AUTHOR: Wang Xin; Zhu Shan; Drozda Martin; Zhang Wenhua; Stavrovskaya Irina G; Cattaneo Elena; Ferrante Robert J; Kristal Bruce S; Friedlander Robert M
CORPORATE SOURCE: Neuroapoptosis Laboratory, Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2003 Sep 2) 100 (18) 10483-7. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030904
Last Updated on STN: 20031024
Entered Medline: 20031023

ABSTRACT:
Minocycline is broadly protective in neurologic disease models featuring cell death and is being evaluated in clinical trials. We previously demonstrated that minocycline-mediated protection against caspase-dependent cell death related to its ability to prevent mitochondrial cytochrome c release. These results do not explain whether or how minocycline protects against caspase-independent cell death. Furthermore, there is no information on whether Smac/Diablo or apoptosis-inducing factor might play a role in chronic neurodegeneration. In a striatal cell model of Huntington's disease and in R6/2 mice, we demonstrate the association of cell death/disease progression with the recruitment of mitochondrial caspase-independent (apoptosis-inducing factor) and caspase-dependent (Smac/Diablo and cytochrome c) triggers. We show that minocycline is a drug that directly inhibits both caspase-independent and -dependent mitochondrial cell death pathways. Furthermore, this report demonstrates recruitment of Smac/Diablo and apoptosis-inducing factor in chronic neurodegeneration. Our results further delineate the mechanism by which minocycline mediates its remarkably broad neuroprotective effects.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Animals
Carrier Proteins: ME, metabolism
*Caspases: AI, antagonists & inhibitors
Caspases: PH, physiology
Cell Death: DE, drug effects
Cell Line
Disease Models, Animal
***Huntington Disease: DT, drug therapy**
**Huntington Disease: PA, pathology**
Mice
*Minocycline: PD, pharmacology
*Mitochondria: DE, drug effects
Mitochondria: PH, physiology
*Neuroprotective Agents: PD, pharmacology
Tumor Necrosis Factor: PH, physiology
CAS REGISTRY NO.: **10118-90-8 (Minocycline)**
CHEMICAL NAME: 0 (BID protein); 0 (Carrier Proteins); 0 (Neuroprotective Agents); 0 (Tumor Necrosis Factor); EC 3.4.22.- (Caspases)

L89 ANSWER 10 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003382197 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12891671

TITLE: Minocycline and doxycycline are not beneficial in a model of Huntington's disease.
COMMENT: Comment in: Ann Neurol. 2003 Dec;54(6):841-2. PubMed ID: 14681898
Comment in: Ann Neurol. 2003 Dec;54(6):841; author reply 842-3. PubMed ID: 14681897
AUTHOR: Smith Donna L; Woodman Benjamin; Mahal Amarbirpal; Sathasivam Kirupa; Ghazi-Noori Shabnam; Lowden Philip A S; Bates Gillian P; Hockly Emma
CORPORATE SOURCE: Department of Medical and Molecular Genetics, King's College London, United Kingdom.
SOURCE: Annals of neurology, (2003 Aug) 54 (2) 186-96.
Journal code: 7707449. ISSN: 0364-5134.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20030816
Last Updated on STN: 20040106
Entered Medline: 20040105

ABSTRACT:
Huntington's Disease (HD) is an inherited neurological disorder causing movement impairment, personality changes, dementia, and premature death, for which there is currently no effective therapy. The modified tetracycline antibiotic, minocycline, has been reported to ameliorate the disease phenotype in the R6/2 mouse model of HD. Because the tetracyclines have also been reported to inhibit aggregation in other amyloid disorders, we have investigated their ability to inhibit huntingtin aggregation and further explored their efficacy in preclinical mouse trials. We show that tetracyclines are potent inhibitors of huntingtin aggregation in a hippocampal slice culture model of HD at an effective concentration of 30 microM. However, despite achieving tissue levels approaching this concentration by oral treatment of R6/2 mice with minocycline, we observed no clear difference in their behavioral abnormalities, or in aggregate load postmortem. In the light of these new data, we would advise that caution be exercised in proceeding into human clinical trials of minocycline.

CONTROLLED TERM: Check Tags: Female; In Vitro; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.
Animals
*Anti-Bacterial Agents: TU, therapeutic use
Behavior, Animal: DE, drug effects
*Doxycycline: TU, therapeutic use
Genotype
Hippocampus: ME, metabolism
Hippocampus: PA, pathology
***Huntington Disease: DT, drug therapy**
**Huntington Disease: GE, genetics**
**Huntington Disease: PA, pathology**
Hyperglycemia: BL, blood
Immunohistochemistry
Mice
*Minocycline: TU, therapeutic use
Musculoskeletal Equilibrium: DE, drug effects
Nerve Tissue Proteins: GE, genetics
Nerve Tissue Proteins: ME, metabolism
Nuclear Proteins: GE, genetics
Nuclear Proteins: ME, metabolism
Organ Culture
Peptides: ME, metabolism
Phenotype
Tetracycline: PD, pharmacology

CAS REGISTRY NO.: **10118-90-8 (Minocycline)**; 26700-71-0 (polyglutamine); 564-25-0 (Doxycycline); 60-54-8 (Tetracycline)
CHEMICAL NAME: 0 (Anti-Bacterial Agents); 0 (Huntingtin protein, human); 0 (Nerve Tissue Proteins); 0 (Nuclear Proteins); 0 (Peptides)

L89 ANSWER 11 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003337088 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12869810
TITLE: Huntington's disease: prospects for neuroprotective therapy 10 years after the discovery of the causative genetic mutation.
AUTHOR: Hersch Steven M
CORPORATE SOURCE: Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA.. Hersch@helix.mgh.harvard.edu
CONTRACT NUMBER: AT00613 (NCCAM)
NS045242 (NINDS)
NS35255 (NINDS)
SOURCE: Current opinion in neurology, (2003 Aug) 16 (4) 501-6. Ref: 64
Journal code: 9319162. ISSN: 1350-7540.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20030719
Last Updated on STN: 20031218
Entered Medline: 20031118

ABSTRACT:
PURPOSE OF REVIEW: Ten years of intensive research are now beginning to bring candidate neuroprotective therapies to clinical trials. This review describes recent progress in basic, preclinical, and clinical research that underlies current and potential neuroprotective trials. RECENT FINDINGS: Basic research continues to elucidate the proteolytic processing of huntingtin into toxic fragments and has examined the toxic potential of huntingtin monomers versus oligomers versus insoluble aggregates. Energy depletion has been reinvigorated as a therapeutic target by studies identifying very early mitochondrial alterations. Toxic interactions between mutant huntingtin and a variety of transcription factors have emerged as a major focus with a variety of studies suggesting transcriptional dysfunction to be a central mechanism in Huntington's disease. Progress in preclinical research included therapeutic leads identified by compound library screens, by designing polypeptides that can interact with huntingtin, and by testing compounds in transgenic mice with the potential for affecting some of the mechanisms thought to underlie neurodegeneration. While early results of neurotransplantation are generating increasing controversy, a variety of compounds discovered to benefit transgenic mice are working their way into clinical trials in symptomatic patients. Studies in presymptomatic individuals at risk for developing Huntington's disease are underway to enable the testing of agents with the potential for delaying or preventing onset of symptoms. SUMMARY: While laboratory research continues to advance and provide therapeutic leads, clinical trials are needed to test existing leads and guide further progress. With any luck, some of these tests will begin to identify treatments that make a difference for families with the disease.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Amantadine: TU, therapeutic use
*Anti-Dyskinesia Agents: TU, therapeutic use

*Antiparkinson Agents: TU, therapeutic use
*Fatty Acids, Unsaturated: TU, therapeutic use
***Huntington Disease: DT, drug therapy**
***Huntington Disease: GE, genetics**
**Huntington Disease: PA, pathology**
Nerve Degeneration: PA, pathology
Nerve Tissue Proteins: GE, genetics
*Neuroprotective Agents: TU, therapeutic use
Nuclear Proteins: GE, genetics
*Point Mutation: GE, genetics
*Riluzole: TU, therapeutic use
*Tetrabenazine: TU, therapeutic use
Time Factors

CAS REGISTRY NO.: **1744-22-5 (Riluzole)**; 58-46-8 (Tetrabenazine); 768-94-5 (Amantadine)

CHEMICAL NAME: 0 (Anti-Dyskinesia Agents); 0 (Antiparkinson Agents); 0 (Fatty Acids, Unsaturated); 0 (Huntingtin protein, human); 0 (Nerve Tissue Proteins); 0 (Neuroprotective Agents); 0 (Nuclear Proteins); 0 (eicosapentanoic acid)

L89 ANSWER 12 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003337082 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12869804
TITLE: Experimental therapeutics in Huntington's disease: are models useful for therapeutic trials?.
AUTHOR: Bates Gillian P; Hockly Emma
CORPORATE SOURCE: King's College London, Guy's Hospital, London SE1 9RT, UK.. gillian.bates@kcl.ac.uk
SOURCE: Current opinion in neurology, (2003 Aug) 16 (4) 465-70. Ref: 44
Journal code: 9319162. ISSN: 1350-7540.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20030719
Last Updated on STN: 20031218
Entered Medline: 20031118

ABSTRACT:
PURPOSE OF REVIEW: Research conducted over the past 10 years has uncovered molecular mechanisms that are likely to be important in the early stages of Huntington's disease pathogenesis. This review summarizes the resources and strategies that are in place in order to exploit these new findings and use them to develop novel Huntington's disease therapeutics. The role that disease models will play in this process is discussed. RECENT FINDINGS: A wide variety of models of Huntington's disease have been developed including yeast, Caenorhabditis elegans, Drosophila melanogaster and mouse. These can be developed as screening assays for the identification of chemical compounds that show beneficial effects against a specific phenotype and for the cross validation of potential therapeutics. The first compounds arising through this drug development pipeline have been reported. Similarly, the preclinical screening of compounds in mouse models is being developed in a coordinated manner. SUMMARY: Our understanding of the molecular basis of Huntington's disease is increasing at an exponential rate. Over the next few years an increasing number of potential therapeutic compounds will have been identified. It will only be possible to take a small number of these through to phase III clinical trials. The challenge will be to use the in-vivo models of Huntington's disease to best predict which of these compounds should be pursued in the clinic, to avoid depleting the patient population willing to enter into

trials, and demoralizing them by conducting repeated unsuccessful trials.
CONTROLLED TERM: Check Tags: Support, Non-U.S. Gov't
*Acetamides: TU, therapeutic use
Animals
*Antioxidants: TU, therapeutic use
*Creatine: TU, therapeutic use
*Disease Models, Animal
Evaluation Studies
***Huntington Disease: DT, drug therapy**
**Huntington Disease: GE, genetics**
Mice
Mice, Transgenic
Nerve Tissue Proteins: GE, genetics
*Neuroprotective Agents: TU, therapeutic use
Nuclear Proteins: GE, genetics
Peptides: GE, genetics
Point Mutation: GE, genetics
*Riluzole: TU, therapeutic use
*Thioctic Acid: TU, therapeutic use
Trinucleotide Repeats: GE, genetics
*Ubiquinone: TU, therapeutic use
CAS REGISTRY NO.: 128298-28-2 (remacemide); 1339-63-5 (Ubiquinone); **1744-22-5 (Riluzole)**; 26700-71-0 (polyglutamine); 57-00-1 (Creatine); 62-46-4 (Thioctic Acid)
CHEMICAL NAME: 0 (Acetamides); 0 (Antioxidants); 0 (Huntingtin protein, human); 0 (Nerve Tissue Proteins); 0 (Neuroprotective Agents); 0 (Nuclear Proteins); 0 (Peptides)

L89 ANSWER 13 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003241953 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12763180
TITLE: [Cutaneous nodules to an aquarist].
Des nodules cutanes chez un aquariophile.
AUTHOR: Sene D; Costedoat N; Barete S; Ayoub N; Piette J-C; Cacoub P
CORPORATE SOURCE: Service de medecine interne, centre hospitalier universitaire Pitie-Salpetriere, 47-83 boulevard de l'hopital, 75651 Paris cedex 13, France.
SOURCE: La Revue de medecine interne / fondee ... par la Societe nationale francaise de medecine interne, (2003 May) 24 (5) 328-9.
Journal code: 8101383. ISSN: 0248-8663.
PUB. COUNTRY: France
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030524
Last Updated on STN: 20030821
Entered Medline: 20030820
CONTROLLED TERM: Check Tags: Human; Male
Animals
*Animals, Domestic: MI, microbiology
Anti-Bacterial Agents: TU, therapeutic use
Antibiotics, Antitubercular: TU, therapeutic use
Diabetes Mellitus, Type II: CO, complications
Drug Resistance, Bacterial
*Fishes: MI, microbiology
*Hand Dermatoses: DI, diagnosis
Hand Dermatoses: DT, drug therapy
*Hand Dermatoses: MI, microbiology

Middle Aged
Minocycline: TU, therapeutic use
*Mycobacterium Infections, Atypical: DI, diagnosis
Mycobacterium Infections, Atypical: DT, drug therapy
*Mycobacterium Infections, Atypical: MI, microbiology
*Mycobacterium marinum
Rifampin: TU, therapeutic use
Risk Factors
*Skin Diseases, Bacterial: DI, diagnosis
Skin Diseases, Bacterial: DT, drug therapy
*Skin Diseases, Bacterial: MI, microbiology
**Spinocerebellar Degenerations: CO, complications**
*Water Microbiology
CAS REGISTRY NO.: **10118-90-8 (Minocycline)**; 13292-46-1 (Rifampin)
CHEMICAL NAME: 0 (Anti-Bacterial Agents); 0 (Antibiotics, Antitubercular)

L89 ANSWER 14 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003157586 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12672865
TITLE: Apoptosis and caspases in neurodegenerative diseases.
AUTHOR: Friedlander Robert M
CORPORATE SOURCE: Neuroapoptosis Laboratory, Division of Cerebrovascular Surgery, Department of Neurosurgery, Brigham and Women's Hospital and Harvard Medical School, Boston 02115, USA.. rfriedlander@rics.bwh.harvard.edu
SOURCE: New England journal of medicine, (2003 Apr 3) 348 (14) 1365-75. Ref: 98
Journal code: 0255562. ISSN: 1533-4406.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030404
Last Updated on STN: 20030410
Entered Medline: 20030409
CONTROLLED TERM: Check Tags: Human
Acute Disease
Amyotrophic Lateral Sclerosis: DT, drug therapy
Amyotrophic Lateral Sclerosis: EN, enzymology
Animals
Anti-Bacterial Agents: TU, therapeutic use
Apoptosis: DE, drug effects
*Apoptosis: PH, physiology
*Caspases: ME, metabolism
Cytochrome c Group: AI, antagonists & inhibitors
Cytochrome c Group: ME, metabolism
**Huntington Disease: DT, drug therapy**
**Huntington Disease: ME, metabolism**
Mice
Minocycline: TU, therapeutic use
Neurodegenerative Diseases: DT, drug therapy
Neurodegenerative Diseases: EN, enzymology
*Neurodegenerative Diseases: PP, physiopathology
CAS REGISTRY NO.: **10118-90-8 (Minocycline)**
CHEMICAL NAME: 0 (Anti-Bacterial Agents); 0 (Cytochrome c Group); EC 3.4.22.- (Caspases)

L89 ANSWER 15 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003116062 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12629257
TITLE: Minocycline for Huntington's disease: an open label study.
AUTHOR: Bonelli Raphael M; Heuberger Clemens; Reisecker Franz
CORPORATE SOURCE: Department of Neurology and Psychiatry, Hospital BHB Eggenberg, Graz, Austria.. rm.bonelli@nextra.at
SOURCE: Neurology, (2003 Mar 11) 60 (5) 883-4.
Journal code: 0401060. ISSN: 1526-632X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20030312
Last Updated on STN: 20040210
Entered Medline: 20040209
CONTROLLED TERM: Check Tags: Female; Human; Male
Activities of Daily Living
Adult
*Caspases: AI, antagonists & inhibitors
Double-Blind Method
**Huntington Disease: CL, classification**
***Huntington Disease: DT, drug therapy**
*Minocycline: TU, therapeutic use
Single-Blind Method
Treatment Outcome
CAS REGISTRY NO.: **10118-90-8 (Minocycline)**
CHEMICAL NAME: EC 3.4.22.- (Caspases)

L89 ANSWER 16 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003069587 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12458211
TITLE: Cystamine inhibits caspase activity. Implications for the treatment of polyglutamine disorders.
AUTHOR: Lesort Mathieu; Lee Matthew; Tucholski Janusz; Johnson Gail V W
CORPORATE SOURCE: Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, 35294-0017, USA.. mlesort@uab.edu
CONTRACT NUMBER: AG12396 (NIA)
NS41552 (NINDS)
SOURCE: Journal of biological chemistry, (2003 Feb 7) 278 (6) 3825-30.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030214
Last Updated on STN: 20030322
Entered Medline: 20030321
ABSTRACT:
Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an abnormally expended polyglutamine domain. There is no effective treatment for HD; however, inhibition of caspase activity or prevention of mitochondria dysfunction delays disease progression in HD mouse models. Similarly administration of cystamine, which can inhibit transglutaminase, prolonged survival of HD mice, suggesting that inhibition of transglutaminase might provide a new treatment strategy. However, it has been suggested that cystamine may inhibit other thiol-dependent enzymes in addition to

transglutaminase. In this study we show that cystamine inhibits recombinant active caspase-3 in a concentration-dependent manner. At low concentrations cystamine is an uncompetitive inhibitor of caspase-3 activity, becoming a non-competitive inhibitor at higher concentrations. The IC(50) for cystamine-mediated inhibition of caspase-3 activity in vitro was 23.6 microm. In situ cystamine inhibited in a concentration-dependent manner the activation of caspase-3 by different pro-apoptotic agents. Additionally, cystamine inhibited caspase-3 activity to the same extent in cell lines stably overexpressing wild type tissue transglutaminase (tTG), a mutant inactive tTG, or an antisense for tTG, demonstrating that cystamine inhibits caspase activity independently of any effects it may have on the transamidating activity of tTG. Finally, treatment with cystamine resulted in a robust increase in the levels of glutathione. These findings demonstrate that cystamine may prolong neuronal survival and delay the onset of HD by inhibiting caspases and increasing the level of antioxidants such as glutathione.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Caspases: AI, antagonists & inhibitors
Caspases: ME, metabolism
*Cystamine: PD, pharmacology
Cystamine: TU, therapeutic use
*Cysteine Proteinase Inhibitors: PD, pharmacology
Cysteine Proteinase Inhibitors: TU, therapeutic use
Enzyme Activation
***Huntington Disease: DT, drug therapy**
**Huntington Disease: EN, enzymology**
Hydrogen Peroxide: PD, pharmacology
*Peptides: ME, metabolism
Tumor Cells, Cultured

CAS REGISTRY NO.: 26700-71-0 (polyglutamine); **51-85-4 (Cystamine)**; 7722-84-1 (Hydrogen Peroxide)

CHEMICAL NAME: 0 (Cysteine Proteinase Inhibitors); 0 (Peptides); EC 3.4.22.- (Caspases); EC 3.4.22.- (caspase-3)

L89 ANSWER 17 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003064038 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12574425
TITLE: Transient and progressive electrophysiological alterations in the corticostriatal pathway in a mouse model of Huntington's disease.
AUTHOR: Cepeda Carlos; Hurst Raymond S; Calvert Christopher R; Hernandez-Echeagaray Elizabeth; Nguyen Oanh K; Jocoy Emily; Christian Lindsey J; Ariano Marjorie A; Levine Michael S
CORPORATE SOURCE: Mental Retardation Research Center, University of California at Los Angeles, Los Angeles, California 90095, USA.
CONTRACT NUMBER: NS 41574 (NINDS)
SOURCE: Journal of neuroscience : official journal of the Society for Neuroscience, (2003 Feb 1) 23 (3) 961-9.
Journal code: 8102140. ISSN: 1529-2401.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20030208
Last Updated on STN: 20030222
Entered Medline: 20030221

ABSTRACT:
Alterations in the corticostriatal pathway may precede symptomatology and striatal cell death in Huntington's disease (HD) patients. Here we examined spontaneous EPSCs in striatal medium-sized spiny neurons in slices from a mouse

model of HD (R6/2). Spontaneous EPSC frequency was similar in young (3-4 weeks) transgenics and controls but decreased significantly in transgenics when overt behavioral symptoms began (5-7 weeks) and was most pronounced in severely impaired transgenics (11-15 weeks). These differences were maintained after bicuculline or tetrodotoxin, indicating they were specific to glutamatergic input and likely presynaptic in origin. Decreases in presynaptic and postsynaptic protein markers, synaptophysin and postsynaptic density-95, occurred in 11-15 week R6/2 mice, supporting the electrophysiological results. Furthermore, isolated, large-amplitude synaptic events (>100 pA) occurred more frequently in transgenic animals, particularly at 5-7 weeks, suggesting additional dysregulation of cortical inputs. Large events were blocked by tetrodotoxin, indicating a possible cortical origin. Addition of bicuculline and 4-aminopyridine facilitated the occurrence of large events. Riluzole, a compound that decreases glutamate release, reduced these events. Together, these observations indicate that both progressive and transient alterations occur along the corticostriatal pathway in experimental HD. These alterations are likely to contribute to the selective vulnerability of striatal medium-sized spiny neurons.

CONTROLLED TERM: Check Tags: In Vitro; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Animals
Cerebral Cortex: DE, drug effects
*Cerebral Cortex: PP, physiopathology
Corpus Striatum: DE, drug effects
*Corpus Striatum: PP, physiopathology
Disease Models, Animal
Disease Progression
Electrophysiology
Excitatory Amino Acid Antagonists: PD, pharmacology
Excitatory Postsynaptic Potentials: DE, drug effects
GABA Antagonists: PD, pharmacology
Glutamic Acid: ME, metabolism
***Huntington Disease: PP, physiopathology**
Mice
Neural Pathways: DE, drug effects
*Neural Pathways: PP, physiopathology
Neurons: DE, drug effects
Neurons: ME, metabolism
Neuroprotective Agents: PD, pharmacology
Patch-Clamp Techniques
Potassium Channel Blockers: PD, pharmacology
Riluzole: PD, pharmacology
Tetrodotoxin: PD, pharmacology

CAS REGISTRY NO.: **1744-22-5 (Riluzole)**; 4368-28-9 (Tetrodotoxin); 56-86-0 (Glutamic Acid)

CHEMICAL NAME: 0 (Excitatory Amino Acid Antagonists); 0 (GABA Antagonists); 0 (Neuroprotective Agents); 0 (Potassium Channel Blockers)

L89 ANSWER 18 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003055877 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12567160
TITLE: Minocycline and other tetracycline derivatives: a neuroprotective strategy in Parkinson's disease and Huntington's disease.
COMMENT: Comment in: Clin Neuropharmacol. 2003 Sep-Oct;26(5):223-4; author reply 224. PubMed ID: 14520158
AUTHOR: Thomas Madhavi; Le Wei Dong; Jankovic Joseph
CORPORATE SOURCE: Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas 77030, USA.
SOURCE: Clinical neuropharmacology, (2003 Jan-Feb) 26 (1) 18-23.

Ref: 62
Journal code: 7607910. ISSN: 0362-5664.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030205
Last Updated on STN: 20030410
Entered Medline: 20030409
CONTROLLED TERM: Check Tags: Human
Animals
Brain: DE, drug effects
Brain: PA, pathology
***Huntington Disease: DT, drug therapy**
**Huntington Disease: PA, pathology**
Minocycline: AE, adverse effects
Minocycline: TU, therapeutic use
Neuroprotective Agents: AE, adverse effects
*Neuroprotective Agents: TU, therapeutic use
*Parkinson Disease: DT, drug therapy
Parkinson Disease: PA, pathology
Tetracyclines: AE, adverse effects
*Tetracyclines: TU, therapeutic use
CAS REGISTRY NO.: **10118-90-8 (Minocycline)**
CHEMICAL NAME: 0 (Neuroprotective Agents); 0 (Tetracyclines)

L89 ANSWER 19 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2003034025 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12540902
TITLE: Pivotal role of oligomerization in expanded polyglutamine neurodegenerative disorders.
AUTHOR: Sanchez Ivelisse; Mahlke Christian; Yuan Junying
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115, USA.
SOURCE: Nature, (2003 Jan 23) 421 (6921) 373-9.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030124
Last Updated on STN: 20030308
Entered Medline: 20030307
ABSTRACT:
The expansion of a CAG repeat coding for polyglutamine in otherwise unrelated gene products is central to eight neurodegenerative disorders including Huntington's disease. It has been well documented that expanded polyglutamine fragments, cleaved from their respective full-length proteins, form microscopically visible aggregates in affected individuals and in transgenic mice. The contribution of polyglutamine oligomers to neurodegeneration, however, is controversial. The azo-dye Congo red binds preferentially to beta-sheets containing amyloid fibrils and can specifically inhibit oligomerization and disrupt preformed oligomers. Here we show that inhibition of polyglutamine oligomerization by Congo red prevents ATP depletion and caspase activation, preserves normal cellular protein synthesis and degradation functions, and promotes the clearance of expanded polyglutamine repeats in vivo and in vitro. Infusion of Congo red into a transgenic mouse model of Huntington's disease, well after the onset of symptoms, promotes the clearance

of expanded repeats in vivo and exerts marked protective effects on survival, weight loss and motor function. We conclude that oligomerization is a crucial determinant in the biochemical properties of expanded polyglutamine that are central to their chronic cytotoxicity.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adenosine Triphosphate: ME, metabolism
Animals
Caspases: ME, metabolism
Cell Death
Congo Red: ME, metabolism
Congo Red: PD, pharmacology
Disease Models, Animal
Enzyme Activation
Hela Cells
**Huntington Disease: EN, enzymology**
**Huntington Disease: GE, genetics**
***Huntington Disease: ME, metabolism**
**Huntington Disease: PP, physiopathology**
Mice
Mice, Transgenic
Neurodegenerative Diseases: EN, enzymology
Neurodegenerative Diseases: GE, genetics
*Neurodegenerative Diseases: ME, metabolism
Neurodegenerative Diseases: PP, physiopathology
Peptides: CH, chemistry
Peptides: GE, genetics
*Peptides: ME, metabolism
Protein Binding: DE, drug effects
Protein Structure, Quaternary: DE, drug effects
Recombinant Fusion Proteins: CH, chemistry
Recombinant Fusion Proteins: GE, genetics
Recombinant Fusion Proteins: ME, metabolism
Survival Rate
*Trinucleotide Repeat Expansion: GE, genetics
Weight Loss: DE, drug effects

CAS REGISTRY NO.: 26700-71-0 (polyglutamine); 56-65-5 (Adenosine Triphosphate); **573-58-0 (Congo Red)**

CHEMICAL NAME: 0 (Peptides); 0 (Recombinant Fusion Proteins); EC 3.4.22.- (Caspases)

L89 ANSWER 20 OF 40 MEDLINE on STN

ACCESSION NUMBER: 2002740329 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12503842

TITLE: Maintained improvement with minocycline of a patient with advanced Huntington's disease.

AUTHOR: Denovan-Wright E M; Devarajan S; Dursun S M; Robertson H A

CORPORATE SOURCE: Department of Pharmacology, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada.

SOURCE: Journal of psychopharmacology (Oxford, England), (2002 Dec) 16 (4) 393-4.
Journal code: 8907828. ISSN: 0269-8811.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200305

ENTRY DATE: Entered STN: 20021231
Last Updated on STN: 20030520
Entered Medline: 20030519

ABSTRACT:

We present the case of a patient with advanced Huntington's disease treated with minocycline. Minocycline (but not tetracycline which does not cross the blood-brain barrier) appears to increase longevity in an animal model for Huntington's disease. The patient has been maintained on minocycline for more than 1 year with positive effects. Cessation of minocyclin for 3 weeks resulted in an exacerbation of symptoms. The animal studies have suggested that minocycline may prevent progression of Huntington's disease and other neurological disorders. By contrast, this present result suggests that minocycline may benefit those with advanced Huntington's disease and can be used safely in these patients.

CONTROLLED TERM: Check Tags: Female; Human
Adult
*Anti-Bacterial Agents: TU, therapeutic use
Antipsychotic Agents: TU, therapeutic use
Apoptosis: DE, drug effects
Clozapine: TU, therapeutic use
***Huntington Disease: DT, drug therapy**
*Minocycline: TU, therapeutic use

CAS REGISTRY NO.: **10118-90-8 (Minocycline)**; 5786-21-0 (Clozapine)

CHEMICAL NAME: 0 (Anti-Bacterial Agents); 0 (Antipsychotic Agents)

L89 ANSWER 21 OF 40 MEDLINE on STN

ACCESSION NUMBER: 2002630582 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12388601

TITLE: Therapeutic effects of cystamine in a murine model of Huntington's disease.

AUTHOR: Dedeoglu Alpaslan; Kubilus James K; Jeitner Thomas M; Matson Samantha A; Bogdanov Misha; Kowall Neil W; Matson Wayne R; Cooper Arthur J L; Ratan Rajiv R; Beal M Flint; Hersch Steven M; Ferrante Robert J

CORPORATE SOURCE: Geriatric Research Education and Clinical Center, Bedford Veterans Affairs Medical Center, Bedford, Massachusetts 01730, USA.

CONTRACT NUMBER: AG 14930 (NIA)
AG12992 (NIA)
AG13846 (NIA)
AT00613 (NCCAM)
NS 38180 (NINDS)
NS 39258 (NINDS)
NS35255 (NINDS)
NS37102 (NINDS)

SOURCE: Journal of neuroscience : official journal of the Society for Neuroscience, (2002 Oct 15) 22 (20) 8942-50.
Journal code: 8102140. ISSN: 1529-2401.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200211

ENTRY DATE: Entered STN: 20021022
Last Updated on STN: 20021213
Entered Medline: 20021125

ABSTRACT:

The precise cause of neuronal death in Huntington's disease (HD) is unknown. Proteolytic products of the huntingtin protein can contribute to toxic cellular aggregates that may be formed in part by tissue transglutaminase (Tgase). Tgase activity is increased in HD brain. Treatment in R6/2 transgenic HD mice, using the transglutaminase inhibitor cystamine, significantly extended survival, improved body weight and motor performance, and delayed the neuropathological sequela. Tgase activity and N(Sigma)-(gamma-L-glutamyl)-L-lysine (GGEL) levels were significantly altered in HD mice. Free GGEL, a specific biochemical marker of Tgase activity, was markedly elevated in the

neocortex and caudate nucleus in HD patients. Both Tgase and GGEL immunoreactivities colocalized to huntingtin aggregates. Cystamine treatment normalized transglutaminase and GGEL levels in R6/2 mice. These findings are consistent with the hypothesis that transglutaminase activity may play a role in the pathogenesis of HD, and they identify cystamine as a potential therapeutic strategy for treating HD patients.

CONTROLLED TERM: Check Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Administration, Oral
Aged
Animals
Behavior, Animal: DE, drug effects
Biological Markers: AN, analysis
Body Weight: DE, drug effects
Caudate Nucleus: ME, metabolism
Caudate Nucleus: PA, pathology
*Cystamine: TU, therapeutic use
Dipeptides: AN, analysis
Dipeptides: ME, metabolism
Disease Models, Animal
Enzyme Activation: DE, drug effects
*GTP-Binding Proteins: AI, antagonists & inhibitors
GTP-Binding Proteins: ME, metabolism
***Huntington Disease: DT, drug therapy**
**Huntington Disease: PA, pathology**
**Huntington Disease: PP, physiopathology**
Injections, Intraperitoneal
Mice
Mice, Transgenic
Middle Aged
Motor Activity: DE, drug effects
Neocortex: ME, metabolism
Neocortex: PA, pathology
Neurons: DE, drug effects
Neurons: ME, metabolism
Neurons: PA, pathology
*Neuroprotective Agents: TU, therapeutic use
Survival Rate
*Transglutaminases: AI, antagonists & inhibitors
Transglutaminases: ME, metabolism
Treatment Outcome

CAS REGISTRY NO.: 17105-15-6 (epsilon-(gamma-glutamyl)-lysine); **51-85-4 (Cystamine)**

CHEMICAL NAME: 0 (Biological Markers); 0 (Dipeptides); 0 (Neuroprotective Agents); EC 2.3.2.- (transglutaminase 2); EC 2.3.2.13 (Transglutaminases); EC 3.6.1.- (GTP-Binding Proteins)

L89 ANSWER 22 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2002449611 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12210870
TITLE: Riluzole prolongs survival time and alters nuclear inclusion formation in a transgenic mouse model of Huntington's disease.
AUTHOR: Schiefer Johannes; Landwehrmeyer G Bernhard; Luesse Hans-Gerd; Sprunken Arne; Puls Christiane; Milkereit Anna; Milkereit Eva; Kosinski Christoph M
CORPORATE SOURCE: University Hospital RWTH Aachen, Department of Neurology, Aachen, Germany.
SOURCE: Movement disorders : official journal of the Movement Disorder Society, (2002 Jul) 17 (4) 748-57.
Journal code: 8610688. ISSN: 0885-3185.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20020906
Last Updated on STN: 20021212
Entered Medline: 20021120

ABSTRACT:
Glutamate excitotoxicity has been suggested to contribute to the pathogenesis of Huntington's disease (HD). Riluzole is a substance with glutamate antagonistic properties that is used for neuroprotective treatment in amyotrophic lateral sclerosis and which is currently tested in clinical trials for treatment of HD. R6/2 transgenic mice, which express exon 1 of the human HD gene with an expanded CAG triplet repeat, serve as a well-characterized mouse model for HD with progressing neurological abnormalities and limited survival. We treated R6/2 HD transgenic mice with riluzole orally beginning at a presymptomatic stage until death to investigate its potential neuroprotective effects in this mouse model and found that survival time in the riluzole group was significantly increased in comparison to placebo-treated transgenic controls. Additionally, the progressive weight loss was delayed and significantly reduced by riluzole treatment; behavioral testing of motor coordination and spontaneous locomotor activity, however, showed no statistically significant differences. We also examined the formation of the HD characteristic neuronal intranuclear inclusions (NII) immunohistologically. At a late disease stage, striatal NII from riluzole-treated transgenic mice showed profound changes in ubiquitination, i.e., NII were less ubiquitinated and surrounded by ubiquitinated micro-aggregates. Staining with antibodies directed against the mutated huntingtin revealed no significant difference in this component of NII. Taken together, these data suggest that riluzole is a promising candidate for neuroprotective treatment in human HD.


CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't
Animals
Cell Nucleus: GE, genetics
*Cell Nucleus: PA, pathology
Cell Nucleus: PH, physiology
Cerebral Cortex: PA, pathology
Cerebral Cortex: PP, physiopathology
Corpus Striatum: PA, pathology
Corpus Striatum: PP, physiopathology
*Excitatory Amino Acid Antagonists: PD, pharmacology
Exons
Glutamic Acid: PH, physiology
**Huntington Disease: GE, genetics**
**Huntington Disease: PA, pathology**
***Huntington Disease: PP, physiopathology**
Immunoenzyme Techniques
Mice
Mice, Transgenic
Motor Skills: PH, physiology
Nerve Tissue Proteins: GE, genetics
*Neuroprotective Agents: PD, pharmacology
Nuclear Proteins: GE, genetics
*Riluzole: PD, pharmacology
Survival Analysis
Trinucleotide Repeats
CAS REGISTRY NO.: **1744-22-5 (Riluzole)**; 56-86-0 (Glutamic Acid)
CHEMICAL NAME: 0 (Excitatory Amino Acid Antagonists); 0 (Huntingtin protein, human); 0 (Nerve Tissue Proteins); 0 (Neuroprotective Agents); 0 (Nuclear Proteins)

L89 ANSWER 23 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2002332591 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12075860
TITLE: Apraxia of eyelid closure in Huntington's disease.
AUTHOR: Bonelli R M; Niederwieser G
CORPORATE SOURCE: Department of Neurology and Psychiatry, Hospital BHB Eggenberg, Graz, Austria.. rm.bonelli@nextra.at
SOURCE: Journal of neural transmission (Vienna, Austria : 1996), (2002 Feb) 109 (2) 197-201.
Journal code: 9702341. ISSN: 0300-9564.
PUB. COUNTRY: Austria
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020623
Last Updated on STN: 20021017
Entered Medline: 20021016
ABSTRACT:
We report a patient with genetically confirmed Huntington's disease (HD) presenting apraxia of eyelid closure (AEC). She was unable to close her eyes at command but was able to blink. Chorea and AEC ameliorated significantly during treatment with olanzapine and riluzole, an inhibitor of glutamate release. AEC is reported in progressive supranuclear palsy, Creutzfeldt-Jakob's disease, amyotrophic lateral sclerosis, and as post-stroke AEC. No report on HD is available so far, although oculomotor disturbances are quite common in this disease.
CONTROLLED TERM: Check Tags: Female; Human
*Apraxias: ET, etiology
Drug Therapy, Combination
*Eyelid Diseases: ET, etiology
***Huntington Disease: CO, complications**
**Huntington Disease: DT, drug therapy**
Middle Aged
Neuroprotective Agents: AD, administration & dosage
Neuroprotective Agents: TU, therapeutic use
Pirenzepine: AD, administration & dosage
Pirenzepine: AA, analogs & derivatives
Pirenzepine: TU, therapeutic use
Riluzole: AD, administration & dosage
Riluzole: TU, therapeutic use
Serotonin Uptake Inhibitors: AD, administration & dosage
Serotonin Uptake Inhibitors: TU, therapeutic use
CAS REGISTRY NO.: 132539-06-1 (olanzapine); **1744-22-5 (Riluzole)**; 28797-61-7 (Pirenzepine)
CHEMICAL NAME: 0 (Neuroprotective Agents); 0 (Serotonin Uptake Inhibitors)

L89 ANSWER 24 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2002150124 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11882065
TITLE: Riluzole and olanzapine in Huntington's disease.
AUTHOR: Bonelli Raphael M; Niederwieser G; Diez J; Koltringer P
SOURCE: European journal of neurology : official journal of the European Federation of Neurological Societies, (2002 Mar) 9 (2) 183-4.
Journal code: 9506311. ISSN: 1351-5101.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CASE REPORTS)
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020308
Last Updated on STN: 20020502
Entered Medline: 20020501
CONTROLLED TERM: Check Tags: Female; Human; Male
Adult
*Antipsychotic Agents: AD, administration & dosage
***Huntington Disease: DT, drug therapy**
*Neuroprotective Agents: AD, administration & dosage
*Pirenzepine: AD, administration & dosage
*Pirenzepine: AA, analogs & derivatives
*Riluzole: AD, administration & dosage
CAS REGISTRY NO.: 132539-06-1 (olanzapine); **1744-22-5 (Riluzole)**;
28797-61-7 (Pirenzepine)
CHEMICAL NAME: 0 (Antipsychotic Agents); 0 (Neuroprotective Agents)

L89 ANSWER 25 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2002092463 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11821898
TITLE: Prolonged survival and decreased abnormal movements in transgenic model of Huntington disease, with administration of the transglutaminase inhibitor cystamine.
COMMENT: Erratum in: Nat Med 2002 Mar;8(3):303
AUTHOR: Karpuj Marcela V; Becher Mark W; Springer Joe E; Chabas Dorothee; Youssef Sawsan; Pedotti Rosetta; Mitchell Dennis; Steinman Lawrence
CORPORATE SOURCE: Department of Neurological Sciences, Stanford University, Stanford, California, USA.
CONTRACT NUMBER: R01 18235
SOURCE: Nature medicine, (2002 Feb) 8 (2) 143-9.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020201
Last Updated on STN: 20020518
Entered Medline: 20020503

ABSTRACT:
An expanded polyglutamine domain in huntingtin underlies the pathogenic events in Huntington disease (HD), characterized by chorea, dementia and severe weight loss, culminating in death. Transglutaminase (TGase) may be critical in the pathogenesis, via cross-linking huntingtin. Administration of the TGase competitive inhibitor, cystamine, to transgenic mice expressing exon 1 of huntingtin containing an expanded polyglutamine repeat, altered the course of their HD-like disease. Cystamine given intraperitoneally entered brain where it inhibited TGase activity. When treatment began after the appearance of abnormal movements, cystamine extended survival, reduced associated tremor and abnormal movements and ameliorated weight loss. Treatment did not influence the appearance or frequency of neuronal nuclear inclusions. Unexpectedly, cystamine treatment increased transcription of one of the two genes shown to be neuroprotective for polyglutamine toxicity in Drosophila, dnaj (also known as HDJ1 and Hsp40 in humans and mice, respectively). Inhibition of TGase provides a new treatment strategy for HD and other polyglutamine diseases.
CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Animals
Brain: EN, enzymology
*Cystamine: TU, therapeutic use
*Enzyme Inhibitors: TU, therapeutic use
***Huntington Disease: DT, drug therapy**

Mice
Mice, Transgenic
*Movement Disorders: PC, prevention & control
Survival
*Transglutaminases: AI, antagonists & inhibitors
Transglutaminases: GE, genetics
Weight Loss: DE, drug effects
CAS REGISTRY NO.: **51-85-4 (Cystamine)**
CHEMICAL NAME: 0 (Enzyme Inhibitors); EC 2.3.2.13 (Transglutaminases)

L89 ANSWER 26 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2002078139 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11804649
TITLE: Mouse models of Huntington's disease.
AUTHOR: Menalled Liliana B; Chesselet Marie-Francoise
CORPORATE SOURCE: Dept of Neurology, Reed Neurological Research Center, UCLA School of Medicine, 710 Westwood Plaza, Los Angeles, CA 90095, USA.. mchesselet@mednet.ucla.edu
SOURCE: Trends in pharmacological sciences, (2002 Jan) 23 (1) 32-9. Ref: 69
Journal code: 7906158. ISSN: 0165-6147.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020128
Last Updated on STN: 20021001
Entered Medline: 20020313
ABSTRACT:
Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder. In 1993 the mutation that causes HD was identified as an unstable expansion of CAG repeats in the IT15 gene. Since then one of the most important advances in HD research has been the generation of various mouse models that enable the exploration of early pathological, molecular and cellular abnormalities produced by the mutation. In addition, these models have made it possible to test different pharmacological approaches to delay the onset or slow the progression of HD. In this article, insights gained from mouse models towards the understanding of HD and the design of new therapeutic strategies are discussed.
CONTROLLED TERM: Check Tags: Human
Animals
Creatine: TU, therapeutic use
Dichloroacetate: TU, therapeutic use
Enzyme Inhibitors: TU, therapeutic use
**Huntington Disease: DT, drug therapy**
***Huntington Disease: GE, genetics**
**Huntington Disease: PA, pathology**
Mice
Mice, Knockout
Mice, Transgenic
Minocycline: TU, therapeutic use
*Models, Animal
Mutation
Nerve Tissue Proteins: GE, genetics
Nuclear Proteins: GE, genetics
Proteins: GE, genetics
Trinucleotide Repeat Expansion
CAS REGISTRY NO.: **10118-90-8 (Minocycline)**; 13425-80-4 (Dichloroacetate); 57-00-1 (Creatine)

CHEMICAL NAME: 0 (Enzyme Inhibitors); 0 (Huntingtin protein, human); 0 (IT 15 gene product, human); 0 (Nerve Tissue Proteins); 0 (Nuclear Proteins); 0 (Proteins)

L89 ANSWER 27 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2001701230 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11741397
TITLE: Inhibition of polyglutamine aggregation in R6/2 HD brain slices-complex dose-response profiles.
AUTHOR: Smith D L; Portier R; Woodman B; Hockly E; Mahal A; Klunk W E; Li X J; Wanker E; Murray K D; Bates G P
CORPORATE SOURCE: Division of Medical and Molecular Genetics, GKT School of Medicine, London, United Kingdom.
SOURCE: Neurobiology of disease, (2001 Dec) 8 (6) 1017-26. Journal code: 9500169. ISSN: 0969-9961.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20011220
Last Updated on STN: 20020924
Entered Medline: 20020221

ABSTRACT:
Huntington's disease (HD) is a late onset neurodegenerative disorder caused by a CAG/polyglutamine (polyQ) repeat expansion. PolyQ aggregates can be detected in the nuclei and processes of neurons in HD patients and mouse models prior to the onset of symptoms. The misfolding and aggregation pathway is an important therapeutic target. To better test the efficacy of aggregation inhibitors, we have developed an organotypic slice culture system. We show here that the formation of polyQ aggregates in hippocampal slices established from the R6/2 mouse follows the same prescribed sequence as occurs in vivo. Using this assay, we show that Congo red and chrysamine G can modulate aggregate formation, but show complex dose-response curves. Oral administration of creatine has been shown to delay the onset of all aspects of the phenotype and neuropathology in R6/2 mice. We show here that creatine can similarly inhibit aggregate formation in the slice culture assay.

CONTROLLED TERM: Check Tags: Female; Male; Support, Non-U.S. Gov't
Animals
Benzoates: PD, pharmacology
Biphenyl Compounds: PD, pharmacology
Cells, Cultured
Congo Red: PD, pharmacology
Creatine: PD, pharmacology
Cysteine Endopeptidases: DE, drug effects
Cysteine Endopeptidases: ME, metabolism
Disease Models, Animal
Dose-Response Relationship, Drug
Drug Evaluation, Preclinical
Dyes: PD, pharmacology
Energy Metabolism: DE, drug effects
Energy Metabolism: PH, physiology
*Hippocampus: DE, drug effects
Hippocampus: ME, metabolism
Hippocampus: PA, pathology
**Huntington Disease: DT, drug therapy**
**Huntington Disease: GE, genetics**
**Huntington Disease: ME, metabolism**
Immunohistochemistry
Mice
Mice, Transgenic
Multienzyme Complexes: DE, drug effects

Multienzyme Complexes: ME, metabolism
Nerve Tissue Proteins: DE, drug effects
Nerve Tissue Proteins: GE, genetics
Nerve Tissue Proteins: ME, metabolism
*Neurons: DE, drug effects
Neurons: ME, metabolism
Neurons: PA, pathology
*Neuroprotective Agents: PD, pharmacology
Nuclear Proteins: DE, drug effects
Nuclear Proteins: GE, genetics
Nuclear Proteins: ME, metabolism
Organ Culture
*Peptides: DE, drug effects
Peptides: GE, genetics
Peptides: ME, metabolism
*Protein Folding
*Trinucleotide Repeat Expansion: DE, drug effects
Trinucleotide Repeat Expansion: GE, genetics
Ubiquitin: DE, drug effects
Ubiquitin: GE, genetics
Ubiquitin: ME, metabolism

CAS REGISTRY NO.: 26700-71-0 (polyglutamine); 57-00-1 (Creatine); **573-58-0 (Congo Red)**; 6472-91-9 (chrysamine G)

CHEMICAL NAME: 0 (Benzoates); 0 (Biphenyl Compounds); 0 (Dyes); 0 (Huntingtin protein, human); 0 (Multienzyme Complexes); 0 (Nerve Tissue Proteins); 0 (Neuroprotective Agents); 0 (Nuclear Proteins); 0 (Peptides); 0 (Ubiquitin); EC 3.4.22 (Cysteine Endopeptidases); EC 3.4.25.1 (proteasome endopeptidase complex)

L89 ANSWER 28 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2001645093 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11697523
TITLE: Riluzole in Huntington's disease (HD): an open label study with one year follow up.
AUTHOR: Seppi K; Mueller J; Bodner T; Brandauer E; Benke T; Weirich-Schwaiger H; Poewe W; Wenning G K
CORPORATE SOURCE: Department of Neurology, Innsbruck University Hospital, Austria.
SOURCE: Journal of neurology, (2001 Oct) 248 (10) 866-9.
Journal code: 0423161. ISSN: 0340-5354.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20011108
Last Updated on STN: 20020614
Entered Medline: 20020328

ABSTRACT:
In an open label study, we administered riluzole (50 mg twice a day) to nine patients with genetically confirmed Huntington's disease (HD) (clinical stages 1-3; mean age 46.4 (SD 9.3) years; mean disease duration 8 (SD 3.3) years). The study was designed to evaluate (1) safety and tolerability of riluzole and (2) effects of riluzole on motor impairment, functional disability, cognitive impairment, and behavioral abnormalities using the Unified HD Rating Scale. Patients were evaluated at baseline and after three and twelve months of riluzole therapy. Laboratory tests (hematology and liver enzymes) were repeated monthly. All adverse experiences, reported spontaneously or observed directly by the investigator, were recorded. Riluzole was well tolerated. No increase of serum liver enzymes was seen throughout the study in all but one

patient showing a mild elevation. At three months, mean total motor scale (TMS), mean TMS chorea subscore, and mean total functional capacity scale were significantly improved compared with baseline. At twelve months, however, this beneficial effect on motor status and overall function was not sustained. In contrast, severity and frequency of behavioral dysfunction as well as psychomotor speed assessed by the symbol digit modalities test were improved compared with baseline. Our data suggest that there are transient antichoreatic effects and more sustained effects of riluzole on psychomotor speed and behavior in patients with HD. A double-blind, placebo-controlled trial appears highly warranted to establish definitely the symptomatic versus neuroprotective actions of riluzole in HD.

CONTROLLED TERM: Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Administration, Oral
Adult
Dose-Response Relationship, Drug
Follow-Up Studies
***Huntington Disease: DT, drug therapy**
**Huntington Disease: PX, psychology**
Middle Aged
Neuroprotective Agents: AD, administration & dosage
Neuroprotective Agents: AE, adverse effects
*Neuroprotective Agents: TU, therapeutic use
Psychomotor Performance: PH, physiology
Riluzole: AD, administration & dosage
Riluzole: AE, adverse effects
*Riluzole: TU, therapeutic use

CAS REGISTRY NO.: **1744-22-5 (Riluzole)**

CHEMICAL NAME: 0 (Neuroprotective Agents)

L89 ANSWER 29 OF 40 MEDLINE on STN

ACCESSION NUMBER: 2001524340 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11571359

TITLE: Intoxication with riluzole in Huntington's disease.

AUTHOR: Bodner T; Jenner C; Benke T; Ober A; Seppi K; Fleischhacker W W

CORPORATE SOURCE: Department of Biological Psychiatry, University of Innsbruck, Austria.. thomas.bodner@uklibk.ac.at

SOURCE: Neurology, (2001 Sep 25) 57 (6) 1141-3.
Journal code: 0401060. ISSN: 0028-3878.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200110

ENTRY DATE: Entered STN: 20010926
Last Updated on STN: 20011022
Entered Medline: 20011018

CONTROLLED TERM: Check Tags: Female; Human
Adult
Dose-Response Relationship, Drug
***Huntington Disease: DT, drug therapy**
**Huntington Disease: PX, psychology**
Neuropsychological Tests
*Overdose: DI, diagnosis
Overdose: PX, psychology
*Riluzole: PO, poisoning
Riluzole: TU, therapeutic use
*Suicide, Attempted
Suicide, Attempted: PX, psychology

CAS REGISTRY NO.: **1744-22-5 (Riluzole)**

L89 ANSWER 30 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2001087352 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11036200
TITLE: Amyloid-like inclusions in Huntington's disease.
AUTHOR: McGowan D P; van Roon-Mom W; Holloway H; Bates G P; Mangiarini L; Cooper G J; Faull R L; Snell R G
CORPORATE SOURCE: Department of Anatomy with Radiology, University of Auckland, Private Bag 92019, Symonds Street, Auckland, New Zealand.
SOURCE: Neuroscience, (2000) 100 (4) 677-80.
Journal code: 7605074. ISSN: 0306-4522.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118

ABSTRACT:
Huntington's disease is a progressive, autosomal dominantly inherited, neurodegenerative disease that is characterized by involuntary movements (chorea), cognitive decline and psychiatric manifestations. This is one of a number of late-onset neurodegenerative disorders caused by expanded glutamine repeats, with a likely similar biochemical basis. Immunohistochemical studies on Huntington's disease tissue, using antibodies raised to the N-terminal region of huntingtin (adjacent to the repeat) and ubiquitin, have recently identified neuronal inclusions within densely stained neuronal nuclei, peri-nuclear and within dystrophic neuritic processes. However, the functional significance of inclusions is unknown. It has been suggested that the disease-causing mechanism in Huntington's disease (and the other polyglutamine disorders) is the ability of polyglutamine to undergo a conformational change that can lead to the formation of very stable anti-parallel beta-sheets; more specifically, amyloid structures. We examined, using Congo Red staining and both polarizing and confocal microscopy, post mortem human brain tissue from five Huntington's disease cases, two Alzheimer's disease cases and two normal controls. Brains from five transgenic mice (R6/2)(12) expressing exon 1 of the human huntingtin gene with expanded polyglutamine, and five littermate controls, were also examined by the same techniques. We have shown that some inclusions in Huntington's disease brain tissue possess an amyloid-like structure, suggesting parallels with other amyloid-associated diseases such as Alzheimer's and prion diseases.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't
Alzheimer Disease: ME, metabolism
Alzheimer Disease: PA, pathology
*Amyloid: ME, metabolism
Animals
Birefringence
Brain: ME, metabolism
Brain: PA, pathology
Congo Red
***Huntington Disease: ME, metabolism**
**Huntington Disease: PA, pathology**
Mice
Microscopy, Confocal
Microscopy, Polarization
Neurons: ME, metabolism
Staining and Labeling
CAS REGISTRY NO.: **573-58-0 (Congo Red)**
CHEMICAL NAME: 0 (Amyloid)

L89 ANSWER 31 OF 40 MEDLINE on STN

ACCESSION NUMBER: 2001026166 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11017110
TITLE: Untangling huntingtin's mysteries.
COMMENT: Comment on: Nat Med. 2000 Jul;6(7):797-801. PubMed ID: 10888929
AUTHOR: Anonymous
SOURCE: Nature medicine, (2000 Oct) 6 (10) 1063.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Editorial
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20020924
Entered Medline: 20001116
CONTROLLED TERM: Check Tags: Human
Animals
Caspases: AI, antagonists & inhibitors
Clinical Trials
Foundations: EC, economics
Foundations: OG, organization & administration
***Huntington Disease: ET, etiology**
***Huntington Disease: TH, therapy**
Mice
Minocycline: PD, pharmacology
Nerve Tissue Proteins: GE, genetics
Nuclear Proteins: GE, genetics
CAS REGISTRY NO.: **10118-90-8 (Minocycline)**
CHEMICAL NAME: 0 (Huntingtin protein, human); 0 (Nerve Tissue Proteins); 0 (Nuclear Proteins); EC 3.4.22.- (Caspases)

L89 ANSWER 32 OF 40 MEDLINE on STN
ACCESSION NUMBER: 2000348031 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10888929
TITLE: Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease.
COMMENT: Comment in: Nat Med. 2000 Oct;6(10):1063. PubMed ID: 11017110
AUTHOR: Chen M; Ona V O; Li M; Ferrante R J; Fink K B; Zhu S; Bian J; Guo L; Farrell L A; Hersch S M; Hobbs W; Vonsattel J P; Cha J H; Friedlander R M
CORPORATE SOURCE: Neuroapoptosis Laboratory, Neurosurgical Service, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.
SOURCE: Nature medicine, (2000 Jul) 6 (7) 797-801.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000811
Last Updated on STN: 20010716
Entered Medline: 20000731

ABSTRACT:
Huntington disease is an autosomal dominant neurodegenerative disease with no effective treatment. Minocycline is a tetracycline derivative with proven safety. After ischemia, minocycline inhibits caspase-1 and inducible nitric oxide synthetase upregulation, and reduces infarction. As caspase-1 and nitric

oxide seem to play a role in Huntington disease, we evaluated the therapeutic efficacy of minocycline in the R6/2 mouse model of Huntington disease. We report that minocycline delays disease progression, inhibits caspase-1 and caspase-3 mRNA upregulation, and decreases inducible nitric oxide synthetase activity. In addition, effective pharmacotherapy in R6/2 mice requires caspase-1 and caspase-3 inhibition. This is the first demonstration of caspase-1 and caspase-3 transcriptional regulation in a Huntington disease model.

CONTROLLED TERM: Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Animals
Anti-Bacterial Agents: TU, therapeutic use
*Caspase 1: BI, biosynthesis
*Caspases: BI, biosynthesis
Disease Models, Animal
Disease Progression
Enzyme Activation: DE, drug effects
Evaluation Studies
Gene Expression Regulation
***Huntington Disease: DT, drug therapy**
**Huntington Disease: MO, mortality**
Mice
Mice, Transgenic
*Minocycline: TU, therapeutic use
*Neuroprotective Agents: TU, therapeutic use
Nitric-Oxide Synthase: DE, drug effects
Transcription, Genetic

CAS REGISTRY NO.: **10118-90-8 (Minocycline)**

CHEMICAL NAME: 0 (Anti-Bacterial Agents); 0 (Neuroprotective Agents); EC 1.14.13.- (inducible nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase); EC 3.4.22.- (Caspases); EC 3.4.22.- (caspase-3); EC 3.4.22.36 (Caspase 1)

L89 ANSWER 33 OF 40 MEDLINE on STN

ACCESSION NUMBER: 2000300971 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10829068

TITLE: Inhibition of huntingtin fibrillogenesis by specific antibodies and small molecules: implications for Huntington's disease therapy.

AUTHOR: Heiser V; Scherzinger E; Boeddrich A; Nordhoff E; Lurz R; Schugardt N; Lehrach H; Wanker E E

CORPORATE SOURCE: Max-Planck-Institut fur Molekulare Genetik, Ihnestrassee 73, D-14195 Berlin, Germany.

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2000 Jun 6) 97 (12) 6739-44. Journal code: 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200007

ENTRY DATE: Entered STN: 20000720
Last Updated on STN: 20020924
Entered Medline: 20000713

ABSTRACT:
The accumulation of insoluble protein aggregates in intra and perinuclear inclusions is a hallmark of Huntington's disease (HD) and related glutamine-repeat disorders. A central question is whether protein aggregation plays a direct role in the pathogenesis of these neurodegenerative diseases. Here we show by using a filter retardation assay that the mAb 1C2, which specifically recognizes the elongated polyglutamine (polyQ) stretch in huntingtin, and the chemical compounds Congo red, thioflavine S, chrysamine G,

and Direct fast yellow inhibit HD exon 1 protein aggregation in a dose-dependent manner. On the other hand, potential inhibitors of amyloid-beta formation such as thioflavine T, gossypol, melatonin, and rifampicin had little or no inhibitory effect on huntingtin aggregation in vitro. The results obtained by the filtration assay were confirmed by electron microscopy, SDS/PAGE, and MS. Furthermore, cell culture studies revealed that the Congo red dye at micromolar concentrations reduced the extent of HD exon 1 aggregation in transiently transfected COS cells. Together, these findings contribute to a better understanding of the mechanism of huntingtin fibrillogenesis in vitro and provide the basis for the development of new huntingtin aggregation inhibitors that may be effective in treating HD.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't
Animals
*Antibodies, Monoclonal: TU, therapeutic use
Benzoates: PD, pharmacology
Biphenyl Compounds: PD, pharmacology
COS Cells
Congo Red: PD, pharmacology
Gossypol: PD, pharmacology
***Huntington Disease: TH, therapy**
Melatonin: PD, pharmacology
*Nerve Tissue Proteins: AI, antagonists & inhibitors
*Nuclear Proteins: AI, antagonists & inhibitors
*Peptides: AI, antagonists & inhibitors
Rifampin: PD, pharmacology
Thiazoles: PD, pharmacology

CAS REGISTRY NO.: 13292-46-1 (Rifampin); 2390-54-7 (thioflavin T); 26700-71-0 (polyglutamine); 303-45-7 (Gossypol); **573-58-0 (Congo Red)**; 6472-91-9 (chrysamine G); 73-31-4 (Melatonin)

CHEMICAL NAME: 0 (Antibodies, Monoclonal); 0 (Benzoates); 0 (Biphenyl Compounds); 0 (Huntingtin protein, human); 0 (Nerve Tissue Proteins); 0 (Nuclear Proteins); 0 (Peptides); 0 (Thiazoles)

L89 ANSWER 34 OF 40 MEDLINE on STN
ACCESSION NUMBER: 1999204544 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10190269
TITLE: Carrell-Krusen Symposium invited lecture. Clinical trials in motor neuron diseases.
AUTHOR: Miller R G
CORPORATE SOURCE: California Pacific Medical Center, San Francisco 94115, USA.. rmiller@cooper.cpmc.org
SOURCE: Journal of child neurology, (1999 Mar) 14 (3) 173-9. Ref: 41
Journal code: 8606714. ISSN: 0883-0738.
PUB. COUNTRY: United States
DOCUMENT TYPE: (LECTURES)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990525

ABSTRACT:
Although there is no truly effective disease-specific therapy for any of the motor neuron diseases, rapid progress in our understanding of the pathophysiology of some of these disorders is being made. In addition to progress in neuroscience, clinical trials of agents that appear to slow the progress of at least one of these diseases, amyotrophic lateral sclerosis, are beginning to show promising results. The first clinical trials in spinal

muscular atrophy are currently underway. A number of other developments have raised the quality of clinical trials, which should improve their productivity and efficiency in the future.

CONTROLLED TERM: Check Tags: Female; Human; Male
Acetic Acids: TU, therapeutic use
Adolescent
Adult
*Amyotrophic Lateral Sclerosis: DT, drug therapy
Amyotrophic Lateral Sclerosis: GE, genetics
Animals
Brain-Derived Neurotrophic Factor: TU, therapeutic use
Child
Child, Preschool
*Clinical Trials: ST, standards
Excitatory Amino Acid Antagonists: TU, therapeutic use
Glutamic Acid: DE, drug effects
*Guidelines: ST, standards
Infant
Insulin-Like Growth Factor I: TU, therapeutic use
Mice
Middle Aged
*Motor Neuron Disease: DT, drug therapy
Motor Neuron Disease: GE, genetics
Muscular Atrophy, Spinal: DI, diagnosis
*Muscular Atrophy, Spinal: DT, drug therapy
Muscular Atrophy, Spinal: GE, genetics
Nerve Growth Factors: TU, therapeutic use
Outcome Assessment (Health Care): OG, organization & administration
**Postpoliomyelitis Syndrome: DT, drug therapy**
Riluzole: TU, therapeutic use

CAS REGISTRY NO.: **1744-22-5 (Riluzole)**; 56-86-0 (Glutamic Acid); 60142-96-3 (gabapentin); 67763-96-6 (Insulin-Like Growth Factor I)

CHEMICAL NAME: 0 (Acetic Acids); 0 (Brain-Derived Neurotrophic Factor); 0 (Excitatory Amino Acid Antagonists); 0 (Nerve Growth Factors)

L89 ANSWER 35 OF 40 MEDLINE on STN
ACCESSION NUMBER: 1999190049 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10091628
TITLE: Riluzole therapy in Huntington's disease (HD).
AUTHOR: Rosas H D; Koroshetz W J; Jenkins B G; Chen Y I; Hayden D L; Beal M F; Cudkowicz M E
CORPORATE SOURCE: Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston 02114, USA.
CONTRACT NUMBER: K08NS01896 (NINDS)
M01 RR 01066 (NCRR)
SOURCE: Movement disorders : official journal of the Movement Disorder Society, (1999 Mar) 14 (2) 326-30.
Journal code: 8610688. ISSN: 0885-3185.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 20000303
Entered Medline: 19990615

ABSTRACT:
We conducted a 6-week open-label trial of riluzole (50 mg twice a day) in eight

subjects with Huntington's disease. Subjects were evaluated before riluzole treatment, on treatment, and off treatment with the chorea, dystonia, and total functional capacity (TFC) scores from the Unified Huntington's Disease Rating Scale and magnetic resonance spectroscopy measurements of occipital cortex and basal ganglia lactate levels. Adverse events and safety blood and urine tests were assessed throughout the study. All subjects completed the study and riluzole was well tolerated. The age was 45+/-10.2 years (mean +/- standard deviation) and the disease duration was 6.1+/-4.1 years. The chorea rating score improved by 35% on treatment (p = 0.013) and worsened after discontinuation of treatment (p = 0.026). There were no significant treatment effects on the dystonia or TFC scores. The baseline occipital and basal ganglia lactate levels were elevated in all subjects; there was a trend toward lower lactate/creatine ratios during riluzole treatment in the basal ganglia spectra but not in occipital cortex spectra. Additional clinical studies of riluzole for both symptomatic and neuroprotective benefit in Huntington's disease are warranted.

CONTROLLED TERM: Check Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adult
Basal Ganglia: DE, drug effects
Basal Ganglia: ME, metabolism
Chorea: DT, drug therapy
Excitatory Amino Acid Antagonists: AE, adverse effects
*Excitatory Amino Acid Antagonists: TU, therapeutic use
***Huntington Disease: DT, drug therapy**
**Huntington Disease: ME, metabolism**
Lactic Acid: ME, metabolism
Magnetic Resonance Spectroscopy
Middle Aged
Neuroprotective Agents: AE, adverse effects
*Neuroprotective Agents: TU, therapeutic use
Occipital Lobe: DE, drug effects
Occipital Lobe: ME, metabolism
Pilot Projects
Riluzole: AE, adverse effects
*Riluzole: TU, therapeutic use
Severity of Illness Index
Single-Blind Method
Treatment Outcome

CAS REGISTRY NO.: **1744-22-5 (Riluzole)**; 50-21-5 (Lactic Acid)

CHEMICAL NAME: 0 (Excitatory Amino Acid Antagonists); 0 (Neuroprotective Agents)

L89 ANSWER 36 OF 40 MEDLINE on STN

ACCESSION NUMBER: 1999049381 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9833635

TITLE: Electrophysiology of the neuroprotective agent riluzole on striatal spiny neurons.

AUTHOR: Centonze D; Calabresi P; Pisani A; Marinelli S; Marfia G A; Bernardi G

CORPORATE SOURCE: Clinica Neurologica, Dipartimento Sanita, Universita Tor Vergata, Rome, Italy.

SOURCE: Neuropharmacology, (1998 Aug) 37 (8) 1063-70.
Journal code: 0236217. ISSN: 0028-3908.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199902

ENTRY DATE: Entered STN: 19990316
Last Updated on STN: 20000303
Entered Medline: 19990226

ABSTRACT:
Striatal spiny neurons are selectively vulnerable in Huntington's disease (HD). No effective treatment is available to limit neuronal death in this pathological condition. In an experimental model of HD, a beneficial effect has recently been reported by the neuroprotective agent riluzole. We performed intracellular recordings in order to characterize the electrophysiological effects of this compound on striatal spiny neurons. Riluzole (0.1-100 microM) affected neither the resting membrane potential nor the input resistance/membrane conductance of the recorded cells. Bath application of this pharmacological agent produced a dose-dependent reduction of the number of spikes evoked by long-lasting depolarizing pulses. The EC50 value for this effect was 0.5 microM. Low doses of riluzole selectively reduced the firing frequency in the last part of the depolarizing pulse suggesting a use-dependent action at low concentrations of this compound. Riluzole produced a dose-dependent reduction of the amplitude of the corticostriatal glutamatergic excitatory post-synaptic potentials (EPSPs) with an extrapolated EC50 value of 6 microM. This effect was reversible and maximal at a concentration of 100 microM. Paired-pulse facilitation (PPF) was not affected by riluzole suggesting that the reduction of excitatory transmission was not only caused by a decrease of presynaptic release. Accordingly, riluzole also reduced the amplitude of membrane depolarization induced by exogenous glutamate. The modulatory action of riluzole on the activity of striatal spiny neurons might support the use of this drug in experimental models of excitotoxicity and in the neurodegenerative disorders involving the striatum.

CONTROLLED TERM: Check Tags: Male; Support, Non-U.S. Gov't
Animals
Corpus Striatum: CY, cytology
*Corpus Striatum: DE, drug effects
Disease Models, Animal
Excitatory Postsynaptic Potentials: DE, drug effects
Glutamic Acid: PD, pharmacology
***Huntington Disease: DT, drug therapy**
**Huntington Disease: PA, pathology**
Membrane Potentials: DE, drug effects
*Neurons: DE, drug effects
*Neuroprotective Agents: PD, pharmacology
Patch-Clamp Techniques
Rats
Rats, Wistar
*Riluzole: PD, pharmacology

CAS REGISTRY NO.: **1744-22-5 (Riluzole)**; 56-86-0 (Glutamic Acid)
CHEMICAL NAME: 0 (Neuroprotective Agents)

L89 ANSWER 37 OF 40 MEDLINE on STN
ACCESSION NUMBER: 1998452913 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9781653
TITLE: Rimmed vacuoles with beta-amyloid and ubiquitinated filamentous deposits in the muscles of patients with long-standing denervation (postpoliomyelitis muscular atrophy): similarities with inclusion body myositis.
AUTHOR: Semino-Mora C; Dalakas M C
CORPORATE SOURCE: Neuromuscular Diseases Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: Human pathology, (1998 Oct) 29 (10) 1128-33.
Journal code: 9421547. ISSN: 0046-8177.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106

Last Updated on STN: 19990106
Entered Medline: 19981105

ABSTRACT:
In the chronically denervated muscles of patients with prior paralytic poliomyelitis, there are secondary myopathic features, including endomysial inflammation and rare vacuolated fibers. To assess the frequency and characteristics of the vacuoles and their similarities with those seen in inclusion body myositis (IBM), we examined 58 muscle biopsy specimens from patients with prior paralytic poliomyelitis for (1) the presence of rimmed vacuoles; (2) acid-phosphatase reactivity; (3) Congo-red-positive amyloid deposits; (4) electron microscopy, searching for tubulofilaments; and (5) immunoelectron microscopy, using antibodies against beta-amyloid and ubiquitin. We found vacuolated muscle fibers in 18 of 58 (31%) biopsies, with a mean frequency of 2.06 +/- 0.42 fibers per specimen. The vacuoles contained acid phosphatase-positive material in 6 of the 18 (33.30%) specimens and stained positive for Congo red in five (27.80%). By immunoelectron microscopy, the vacuoles contained 5.17 +/- 0.13 nm fibrils and 14.9 +/- 0.31 nm filaments that immunoreacted with antibodies to beta-amyloid and ubiquitin in a pattern identical to the one seen in IBM. We conclude that vacuolated muscle fibers containing filamentous inclusions positive for amyloid and ubiquitin are not unique to IBM and the other vacuolar myopathies but can also occur in a chronic neurogenic condition, such as postpoliomyelitis. The chronicity of the underlying disease, rather than the cause, may lead to vacuolar formation, amyloid deposition, and accumulation of ubiquitinated filaments.

CONTROLLED TERM: Check Tags: Human
*Amyloid beta-Protein: AN, analysis
Biopsy
Congo Red
Denervation
Immunohistochemistry
Microscopy, Electron
Microscopy, Immunoelectron
Middle Aged
Muscle Fibers: PA, pathology
*Muscles: PA, pathology
*Myositis, Inclusion Body: PA, pathology
***Postpoliomyelitis Syndrome: PA, pathology**
*Ubiquitins: AN, analysis
*Vacuoles: PA, pathology

CAS REGISTRY NO.: **573-58-0 (Congo Red)**
CHEMICAL NAME: 0 (Amyloid beta-Protein); 0 (Ubiquitins)

L89 ANSWER 38 OF 40 MEDLINE on STN
ACCESSION NUMBER: 1998325373 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9660943
TITLE: Transglutaminase action imitates Huntington's disease: selective polymerization of Huntingtin containing expanded polyglutamine.
AUTHOR: Kahlem P; Green H; Djian P
CORPORATE SOURCE: Centre National de la Recherche Scientifique, Centre de Recherche sur l'Endocrinologie Moleculaire et le Developpement, Meudon-Bellevue, France.
CONTRACT NUMBER: MH/NS 31862 (NIMH)
SOURCE: Molecular cell, (1998 Mar) 1 (4) 595-601.
Journal code: 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980811
Last Updated on STN: 20020924

Entered Medline: 19980728

ABSTRACT:
Different proteins bearing polyglutamine of excessive length are lethal to neurons and cause human disease of the central nervous system. In parts of the brain affected by Huntington's disease, the amount of the huntingtin with expanded polyglutamine is reduced and there appear huntingtin-containing polymers of larger molecular weight. We show here that huntingtin is a substrate of transglutaminase in vitro and that the rate constant of the reaction increases with length of the polyglutamine over a range of an order of magnitude. As a result, huntingtin with expanded polyglutamine is preferentially incorporated into polymers. Both disappearance of the huntingtin with expanded polyglutamine and its replacement by polymeric forms are prevented by inhibitors of transglutaminase. The effect of transglutaminase therefore duplicates the changes in the affected parts of the brain.

CONTROLLED TERM: Check Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adolescent
Adult
Age Factors
Cells, Cultured
Cerebral Cortex: CH, chemistry
*Cerebral Cortex: EN, enzymology
Cystamine: PD, pharmacology
***Huntington Disease: EN, enzymology**
Lymphocytes: CY, cytology
Mutagenesis: PH, physiology
Nerve Tissue Proteins: GE, genetics
*Nerve Tissue Proteins: ME, metabolism
Nuclear Proteins: GE, genetics
*Nuclear Proteins: ME, metabolism
*Peptides: ME, metabolism
Protein Binding: DE, drug effects
Substrate Specificity
*Transglutaminases: ME, metabolism
Transglutaminases: PD, pharmacology

CAS REGISTRY NO.: 26700-71-0 (polyglutamine); **51-85-4 (Cystamine)**

CHEMICAL NAME: 0 (Huntingtin protein, human); 0 (Nerve Tissue Proteins); 0 (Nuclear Proteins); 0 (Peptides); EC 2.3.2.13 (Transglutaminases)

L89 ANSWER 39 OF 40 MEDLINE on STN
ACCESSION NUMBER: 97212146 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9082290
TITLE: [Neurodegeneration: aging and dementia. Etiopathogenic role of electron transport disorders. Therapeutic possibilities].
Neurodegeneracio: oregedes es demencia. Elektrontranszport-zavar, mint etiopatogenetikai tenyezo. Terapias lehetosegek.
AUTHOR: Klivenyi P; Vecsei L
CORPORATE SOURCE: Szent-Gyorgyi Albert Orvostudomanyi Egyetem, Szeged.
SOURCE: Orvosi hetilap, (1997 Feb 9) 138 (6) 331-5. Ref: 43
Journal code: 0376412. ISSN: 0030-6002.
PUB. COUNTRY: Hungary
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: Hungarian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970414

Last Updated on STN: 20000303
Entered Medline: 19970328

ABSTRACT:
The neurodegenerative disorders (Parkinson's disease, Alzheimer's dementia, Huntington's disease, cerebellar degeneration) are common medical and social problems. The late onset diseases and slow neurodegeneration is connected with excitotoxins and alteration of mitochondrial electron transport chain. In elderly, congenital and acquired defects of mitochondrial complexes cause formation of free radicals. The overstimulation of excitatory amino acid receptors interfere with the cellular energy metabolism and also forming reactive oxygen species. The impaired energy metabolism make neuronal cells vulnerable to the excitotoxic damage. In these ways, excitotoxicity may be the final common pathway of neuronal death in a variety of neurodegenerative diseases. Potential therapeutic strategies would be use receptor antagonist or drugs to bypass energetic defects.

CONTROLLED TERM: Check Tags: Female; Human; Male
Aged
*Aging
Alzheimer Disease: DT, drug therapy
*Alzheimer Disease: PP, physiopathology
Calcium Channel Blockers: TU, therapeutic use
Cerebellar Diseases: DT, drug therapy
*Cerebellar Diseases: PP, physiopathology
Dementia: DT, drug therapy
*Dementia: PP, physiopathology
Electron Transport
English Abstract
**Huntington Disease: DT, drug therapy**
***Huntington Disease: PP, physiopathology**
Middle Aged
Monoamine Oxidase Inhibitors: TU, therapeutic use
Neuroprotective Agents: TU, therapeutic use
Parkinson Disease: DT, drug therapy
*Parkinson Disease: PP, physiopathology
Riluzole
Thiazoles: TU, therapeutic use
Triazines: TU, therapeutic use

CAS REGISTRY NO.: **1744-22-5 (Riluzole)**; 84057-84-1 (lamotrigine)

CHEMICAL NAME: 0 (Calcium Channel Blockers); 0 (Monoamine Oxidase Inhibitors); 0 (Neuroprotective Agents); 0 (Thiazoles); 0 (Triazines)

L89 ANSWER 40 OF 40 MEDLINE on STN
ACCESSION NUMBER: 86285471 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2874527
TITLE: Huntington's disease: effect of cysteamine, a somatostatin-depleting agent.
AUTHOR: Shults C; Steardo L; Barone P; Mohr E; Juncos J; Serrati C; Fedio P; Tamminga C A; Chase T N
SOURCE: Neurology, (1986 Aug) 36 (8) 1099-102.
Journal code: 0401060. ISSN: 0028-3878.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198609
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 20000303
Entered Medline: 19860917

ABSTRACT:

Somatostatin levels in the basal ganglia are elevated in Huntington's disease. A controlled therapeutic trial of the somatostatin-depleting agent, cysteamine, was therefore conducted in five patients, including one with the rigid-akinetic form. Maximum tolerated dosage for 2 weeks produced no consistent change in extrapyramidal or dementia scores. Somatostatin concentrations were not significantly altered in plasma or CSF. Growth hormone levels, on the other hand, more than doubled, suggesting a functionally significant decrease in central somatostatin levels.

CONTROLLED TERM: Check Tags: Female; Human; Male
Adult
Cognition: DE, drug effects
*Cysteamine: PD, pharmacology
Cysteamine: TU, therapeutic use
**Huntington Disease: DT, drug therapy**
***Huntington Disease: ME, metabolism**
Middle Aged
*Somatostatin: AN, analysis

CAS REGISTRY NO.: 51110-01-1 (Somatostatin); **60-23-1 (Cysteamine)**

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